# Formulation and Evaluation of Gastro-retentive Floating Tablets of an Anti Viral Drug-Famciclovir

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## ABSTRACT

*The aim of the present work is to design floating tablets of Famciclovir to prolong the gastric residence time and oral bioavailability of the drug. Tablets were prepared by wetand melt granulation techniques using alone or different combinations of hydrophilic and lipophilic polymers such as Gelucire 43/01, Gelucire 50/02, Geleol, Compritol 888 ATO, Polyox WSR 303 and HPMC polymers of K 15 and K 100 grades in various concentrations. Prepared formulations were subjected to pre- and post-granulation parameters such as hardness, friability, swelling ability, floating behaviour,drug release and drug-polymer compatibility studies in accordance with ICH guidelines. Results shown that Famciclovir is soluble at pH 1.2, indicating good absorption in the stomach region and by observing the drug release studies FF24 formulation has shown controlled release for 12 hours with less floating lag time of 30 Seconds by using the combination of 0.5:1 ratio of Compritol 888 ATO: HPMC K100 polymers. So, it is concluded that FF24 was selected as optimized formulation as it follows zero order drug release with Higuchi diffusion mechanism.*

Key words: Famciclovir, Gastric residence time.

## INTRODUCTION

Famciclovir is a guanosine analogue antiviral drug, used for the treatment of various herpes virus infections, most commonly shingles caused by herpes zoster andother infections caused by herpes simplex virus. It undergoes rapid biotransformation to the active compound Penciclovir.[1]Because of shortbiological half-life of 2-2.5hrs, Famciclovir eliminates quickly from the body as it undergoes extensive first pass metabolism.[2]Therefore, in order to improve drug bioavailability and to increase the drug residence time, controlled gastric retention system by various mechanismshas chosen.[3,4] Among those,floatingdrugdeliveryapproach have been most commonly used to formulate with different polymers such as Gelucire 43/01, Gelucire 50/02 and Geleolas carrier forming materials, Hydroxypropyl methylcellulose (HPMC) and Ethyl cellulose as controlled release agents, Sodium bicarbonate and Citric acid as gas generating agents and other polymers owing to their low density,hydrophilic lipophilic balance, floating and modified release properties.[5,6]AsFamciclovir is soluble in acidic pH and predominantly get absorbed from the stomach, in the present work an attempt was made to use a combination of (various ratios) hydrophilic and lipophilic polymers to control the release and to increase the gastric residence time of the drug.

## MATERIALS AND METHODS

### Drugs and Excipients

The main drug Famciclovir was obtained as a gift sample from Hetero Drugs Limited, Hyderabad, India. Polymers such as Gelucire 43/01, Gelucire 50/02, Geleol and Compritol 888 ATO were obtained from Gattefosse (St Priest, Cedex, France) as gift samples, Polyox WSR 303 from Aurobindo Pharma Limited,

Hyderabad, India and other polymers such as HPMC, Ethyl cellulose, Sodium bicarbonate, Magnesium Stearate, Talc were purchased from S D Fine Chemicals Limited, Mumbai, India. And all the other reagents used were of analytical grade.

## PRE-FORMULATION STUDIES

Identification of the drug (Famciclovir) by organoleptic evaluation, determination of melting point and solubility profile were carried out as per Indian Pharmacopoeia, 2007 and literature survey. Standard calibration curve of Famciclovir was carried out in 0.1N HCl at 225nm by using UV-Visible spectrophotometer.

### Drug Polymer Compatibility study by FTIR[7,8]

Main purpose of FTIR study is to observe any prominent changes in the spectrum pattern of the drug due to polymers and thus to identify the drug polymer compatibility without any interactions. An IR spectrum of pure drug (Famciclovir) and optimized physical mixture of the Famciclovir with the polymers used was recorded at a range between 500-4000$cm^{-1}$ with a resolution of 4$cm^{-1}$ by using FTIR spectrophotometer.

### Evaluation of Flow properties

Powder form of Famciclovir optimized mixture was evaluated for flow properties by measuring Bulk Density (Cylinder method), Tapped Density (Cylinder method), Angle of Repose (Fixed Funnel method), Compressibility by Carr's index and Hausner's ratio.

## METHODS OF PREPARATION[9-11]

### 1)Wet Granulation Method

Required quantities of drug and polymers were weighed and blendedthoroughly. The blend was granulated by gradually adding 10% of polyvinyl pyrrolidine K30 solution in n-iso propyl alcohol, dropwise. The so formed wet mass was then passed through 16# sieve and dried at ~55$^{\circ}$C for about one hour to getgranules. The granules so obtained were sieved through 10 # sieve and finally compressed into tablets using compression machine after adding sufficient lubricant and glidant.

### 2) Melt Granulation Method

Mentioned quantities of drug and excipients were weighed according to the formulationchart. Respective lipoidal polymers were taken into a beaker and melted for a temperature above 2°C to their corresponding melting points. Previously prepared drug- excipient mixture was added to themolten mass with continuous agitation and allowed to solidify at4°C. The solidified mass was then passed through 16# sieve to attain uniform sizedgranules. The granules so obtained were sieved through 10 # sieve and finally compressed into tablets using compression machine after adding sufficient lubricant and glidant.

Each tablet contained 125mg of Famciclovir. Compositions of different formulations were given in the tables 1, 2 & 3 as shown below;

**Table: 1 Composition of Famciclovir gastroretentive floating tablets from FF1- FF12**

| Ingredients (mg) | FF1-FF12 (Drug: Polymer Ratio) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1:0.25 | | | | 1:0.5 | | | | 1:0.75 | | | |
| | FF1 | FF2 | FF3 | FF4 | FF5 | FF6 | FF7 | FF8 | FF9 | FF10 | FF11 | FF12 |
| **Famciclovir** | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 |
| Gelucire 43/01 | 31.25 | --- | --- | --- | 62.5 | --- | --- | --- | 93.75 | --- | --- | --- |
| Gelucire 50/02 | --- | 31.25 | --- | --- | --- | 62.5 | --- | --- | --- | 93.75 | --- | --- |
| Geleol | --- | --- | 31.25 | --- | --- | --- | 62.5 | **---** | --- | --- | 93.75 | --- |
| Compritol 888 ATO | --- | --- | --- | 31.25 | --- | --- | --- | 62.5 | --- | --- | --- | 93.75 |
| Avicel PH 101 | 93.75 | 93.75 | 93.75 | 93.75 | 62.5 | 62.5 | 62.5 | 62.5 | 31.25 | 31.25 | 31.25 | 31.25 |
| Sodium Bicarbonate | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Citric Acid | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Magnesium Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 2 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 4 | 4 | 4 |
| Total weight (mg) | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**Table: 2 Composition of Famciclovir gastroretentive floating tablets from FF13- FF21**

| Ingredients (mg) | FF13-FF21 (Drug: Polymer Ratio) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1:0.25 | | | 1:0.5 | | | 1:0.75 | | |
| | FF13 | FF14 | FF15 | FF16 | FF17 | FF18 | FF19 | FF20 | FF21 |
| **Famciclovir** | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 |
| Polyox 303 WSR | 31.25 | --- | **---** | 62.5 | --- | --- | 93.75 | --- | --- |
| HPMC K15 | --- | 31.25 | **---** | --- | 62.5 | --- | --- | 93.75 | --- |
| HPMC 100k | --- | --- | 31.25 | --- | --- | 62.5 | --- | --- | 93.75 |
| Avicel PH 101 | 93.75 | 93.75 | 93.75 | 62.5 | 62.5 | 62.5 | 31.25 | 31.25 | 31.25 |
| Sodium Bicarbonate | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Citric Acid | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Magnesium Stearate | 4 | 4 | 4 | 4 | 4 | 4 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 4 | 4 |
| **Total weight (mg)** | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**Table: 3 Composition of Famciclovir gastroretentive floating tablets from FF22- FF24**

| **Ingredients (mg)** | **F22-F24(Drug: Polymer Ratio)** | | |
|---|---|---|---|
| | **1:0.5** | | |
| | **FF22** | **FF23** | **FF24** |
| **Famciclovir** | 125 | 125 | **125** |
| HPMC 100k | 62.5 | 46.9 | **31.25** |
| Compritol 888 ATO | 31.25 | 46.9 | **62.5** |
| Avicel PH 101 | 93.75 | 93.75 | **93.75** |
| Sodium Bicarbonate | 40 | 40 | **40** |
| Citric Acid | 4 | 4 | **4** |
| Magnesium Stearate | 4 | 4 | **4** |
| Talc | 2 | 2 | **2** |
| Total weight (mg) | 300 | 300 | **300** |

## EVALUATION OF TABLETS[12,13]

Prepared tablets of Famciclovir were evaluated for hardness using a Monsanto tablet hardness tester. Friability was determined in a friability tester for 100 revolutions at 25 rpm for 4minutes. Weight variation test was done according to the official pharmacopeial procedure with the specification limit not more than two of the individual weight deviates by 10% of average weight and none should deviate twice that percentage.

### Estimation of DrugContent

The drug content in each formulation was determined in triplicates. For each batch of formulation, 20 tablets were taken, weighed and powdered finely using motor and pestle.100 mg equivalent of tablet powder was weighed and dissolved in 100 ml of pH 1.2 acetate buffer followed by stirring for 10 min and then filtered through 0.45µ membrane filter. The samples were analyzed after necessary dilutions using UV Visible Spectrophotometer.

### *In- vitro* Swelling studies (SI)

To evaluate the water penetration characteristics, prepared floating tablet formulations were weighed individually(W1) and placed separately in a glass beaker containing 200 ml of 0.1 N HCl incubated at 37 ± 1°C. At regular 1 h time interval until 12 h, the tablets were removed from beaker and the excess surface liquid was wiped carefully using the paper. The swollen tablets were then reweighed (W2) and the swelling index (SI) was calculated by the following formula.

% SI = (W2 – W1)/W1*100

### *In-vitro* BuoyancyStudies[14]

Buoyancy of a tablet is determined by its floatinglagtime.Preparedformulationswereplacedina 100 ml glass beaker containing 0.1 N HCl and the time required for each tablet to raise to the surface and float is determined and it is considered as floating lag time and also the total time duration by which a dosage form remain buoyant is determined, it is considered as total floating time.

### *In-vitro* DissolutionStudies

*In- vitro* Drug Release Studies of prepared gastro-retentive formulations was carried out using USP type II Dissolution apparatus (paddle type).Conditionsappliedforthedissolutionstudieswere:900mlof0.1 N HCl (pH 1.2) as media for dissolution, temperature maintained at 37 ±0.5 °C with rotation speed of 50 rpm. 5 ml Aliquot of samples were withdrawn at specific different time intervals and filtered through Millipore 0.45 µ filter. The volume of dissolution fluid is adjusted to 900 ml by replacing 5 ml of dissolution medium after each sampling. Samples were diluted as per need, analyzed for absorbance and cumulative percentage of the drug release was calculated. The mean of cumulative % of the drug released from 6 tablets from different batch of formulations were used for analysis ofdata.

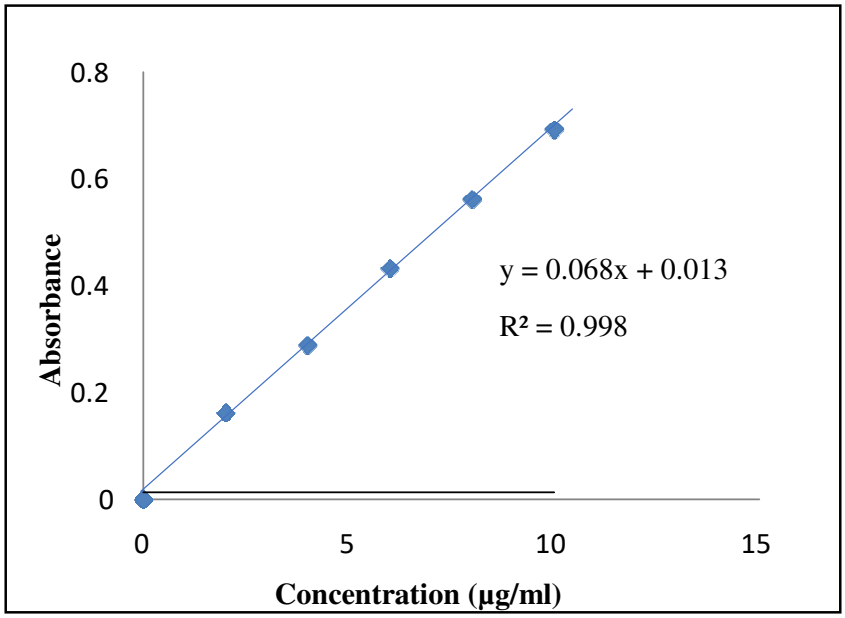
### Kinetic modeling of Drug ReleaseProfiles[15]

To analyze and evaluate the drug release mechanism from the dosage form, the obtained dissolution data of optimized batches was fitted to various kinetic models like zero- order, first-order, Higuchi and Korsmeyer-Peppas equation to ascertain the kinetic modeling of drug release.

## RESULTS AND DISCUSSION

### Figure: 1Calibration Curve ofFamciclovir

Famciclovir solution in 0.1NHCl was scanned at 200-400nm by using UV- Visible Spectrophotometer. It was found that maximum wavelength of Famciclovir is 225 nm in 0.1NHCl.




A linear relationship was established between the Concentration on X-axis vs Absorbance on Y-axis with R² of 0.998.

### Table: 4 Absorbance of Famciclovir at Maximum wavelength

| Concentration (µg/ml) | Absorbance (λmax 225 nm) |
|---|---|
| 0 | 0 |
| 2 | 0.162±0.001 |
| 4 | 0.289±0.009 |
| 6 | 0.432±0.011 |
| 8 | 0.562±0.008 |
| 10 | 0.692±0.006 |

**FTIR study**

There is no prominent difference was observed in the principal IR spectrum of Drug excipient mixture and optimized formulation upon comparison with the peaks of drug and polymer alone, which is considered as drug and polymers were compatible enough without any interactions.

**Figure: 2FTIR Spectrum of Famciclovir**

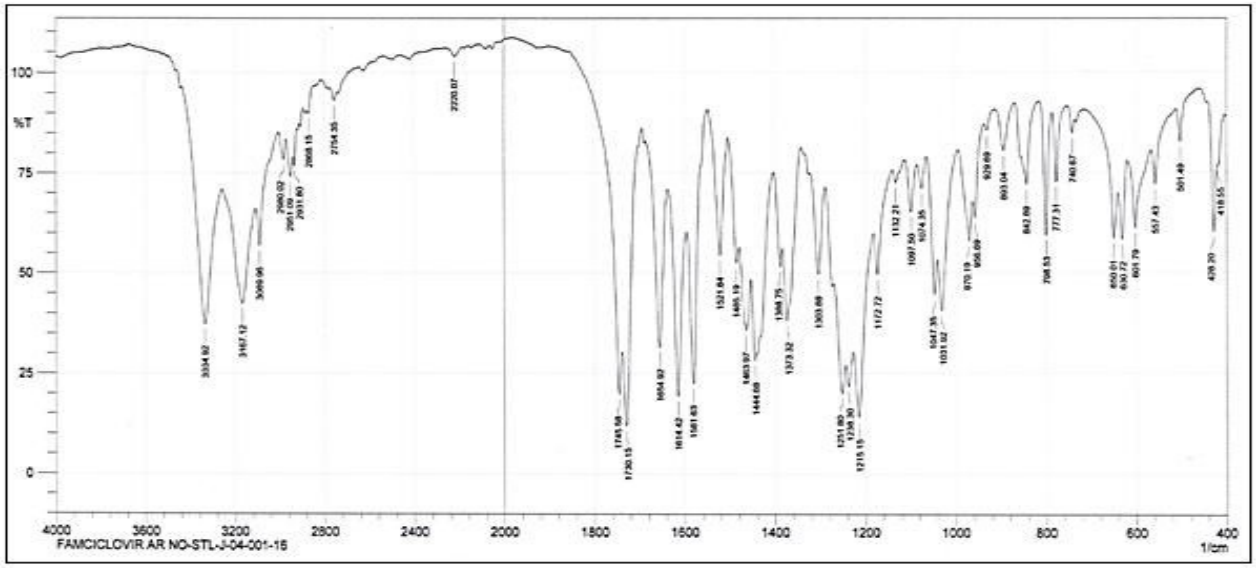



**Table: 5FTIR Spectral data of Famciclovir**

| BOND | FREQUENCY RANGE | OBSERVATION |
|---|---|---|
| NH2 | 3400-3500 cm-1 (Stretching) | 3334.92cm-1 |
| | 1500-1650 cm-1 (Bending) | 1614.42cm-1 |
| C=N | 1630-1690 cm-1 | 1654.92 cm-1 |
| C=O | 1705-1725 cm-1 | 1730.15 cm-1 |
| C=C | 1680-1620 cm-1 | 1654.92 cm-1 |

**Figure: 3FTIR Spectrum of Famciclovir Optimized formulation**

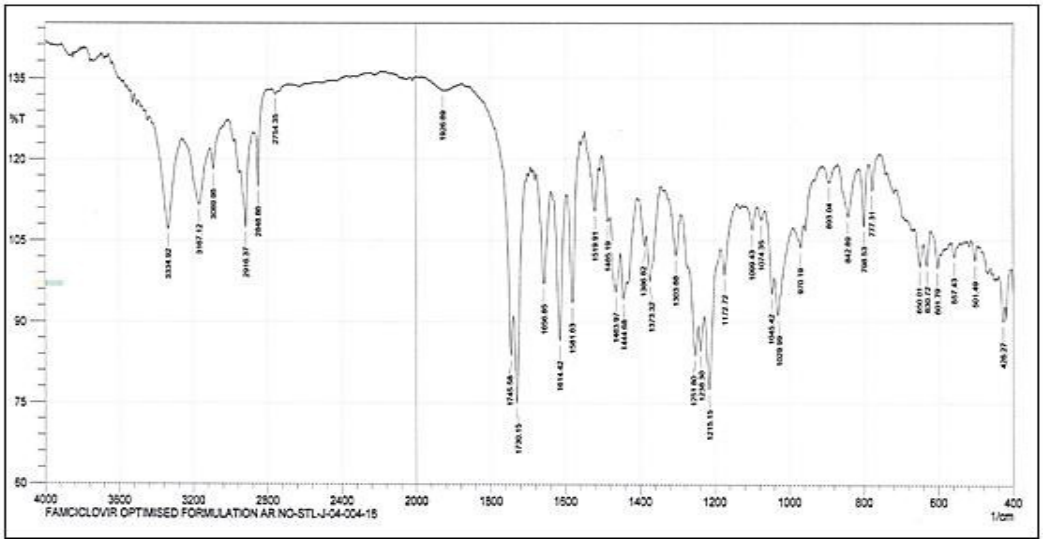



**Table: 6FTIR Spectral data of Famciclovir Optimized formulation**

| BOND | FREQUENCY RANGE | OBSERVATION |
|---|---|---|
| NH2 | 3400-3500 $cm^{-1}$(Stretching)<br>1500-1650 $cm^{-1}$(Bending) | 3334.92$cm^{-1}$<br>1614.42$cm^{-1}$ |
| C=N | 1630-1690 $cm^{-1}$ | 1658.85 $cm^{-1}$ |
| C=O | 1705-1725 $cm^{-1}$ | 1730.15 $cm^{-1}$ |
| C=C | 1680-1620 $cm^{-1}$ | 1658.85 $cm^{-1}$ |

**Evaluation of Flow Properties**

Different flow properties of granules were calculated in the form of Bulk density, Tapped density, Carr's Index, Hausner's ratio and Angle of Repose.

**Table: 7 Evaluation of Flow properties**

| Parameter | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's Ratio | Angle of Repose (º) |
|---|---|---|---|---|---|
| FF1 | 0.520 | 0.613 | 15.17 | 1.17 | 33 |
| FF2 | 0.523 | 0.633 | 17.37 | 1.21 | 29 |
| FF3 | 0.512 | 0.621 | 17.55 | 1.21 | 31 |

| | | | | | |
|---|---|---|---|---|---|
| FF4 | 0.516 | 0.682 | 24.34 | 1.32 | 35 |
| FF5 | 0.502 | 0.659 | 23.8 | 1.31 | 33 |
| FF6 | 0.501 | 0.623 | 19.58 | 1.24 | 32 |
| FF7 | 0.506 | 0.642 | 21.18 | 1.27 | 28 |
| FF8 | 0.511 | 0.678 | 24.63 | 1.32 | 29 |
| FF9 | 0.521 | 0.630 | 17.30 | 1.20 | 31 |
| FF10 | 0.516 | 0.635 | 18.74 | 1.23 | 32 |
| FF11 | 0.532 | 0.645 | 17.51 | 1.21 | 33 |
| FF12 | 0.513 | 0.632 | 18.82 | 1.23 | 34 |
| FF13 | 0.520 | 0.645 | 19.37 | 1.24 | 32 |
| FF14 | 0.512 | 0.630 | 18.73 | 1.23 | 33 |
| FF15 | 0.522 | 0.652 | 19.93 | 1.25 | 34 |
| FF16 | 0.521 | 0.642 | 18.84 | 1.23 | 31 |
| FF17 | 0.513 | 0.623 | 17.65 | 1.21 | 31 |
| FF18 | 0.524 | 0.653 | 19.75 | 1.25 | 30 |
| FF19 | 0.521 | 0.630 | 17.30 | 1.21 | 28 |
| FF20 | 0.523 | 0.653 | 19.90 | 1.25 | 31 |
| FF21 | 0.528 | 0.663 | 20.36 | 1.25 | 29 |
| FF22 | 0.519 | 0.642 | 19.15 | 1.24 | 32 |
| FF23 | 0.523 | 0.635 | 17.63 | 1.21 | 33 |
| FF24 | **0.516** | **0.626** | **17.57** | **1.21** | **32** |

Formulations FF1 to FF24 have shown varying bulk densities between 0.501 to 0.552 gm/ml, tapped density ranging from 0.621to 0.682 gm/ml, also angle of repose, compressibility index and hausner's ratio werewithin the IP limits. All these results indicate that, the powder mixture possess satisfactory flow properties and compressibility.

### Evaluation of Formulated Tablets

Each formulated tablet was analyzed for hardness, weight variation, friability, drug content, floating characteristics and in vitro drug release.

All the formulations passed the weightvariation and friabilitytests, as all the tablets were within the range of limit. Weight loss in the friability test was less than 1% in all the cases. Hardness was in the range of 4.0±0.63 to 5.9±0.69 Kg/cm$^2$, which was due to the presence of waxypolymers. Results were given the table as below

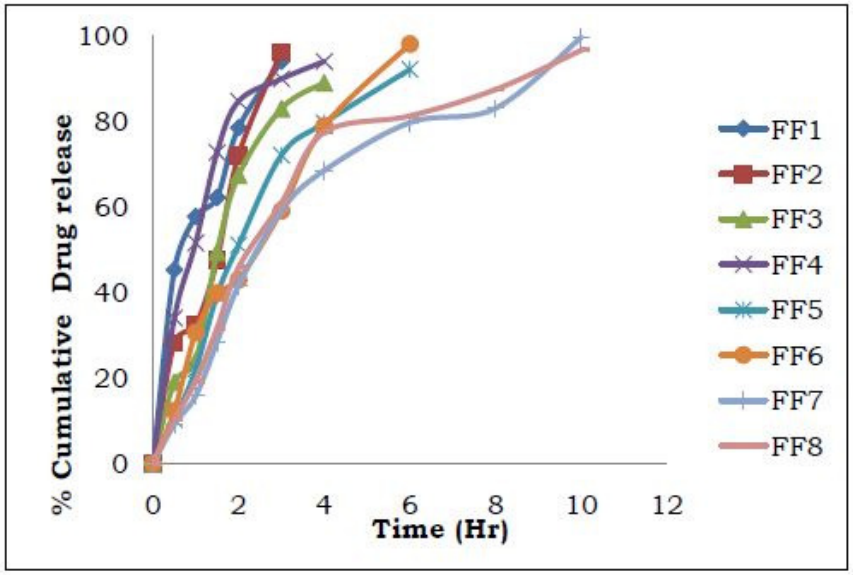
**Table: 8 Evaluation of Formulated Tablets**

| Parameter | Average wt. (mg)(n=10) | Hardness ($Kg/cm^2$) (n=10) | Thickness (mm) (n=10) | Friability % | % Drug content |
|---|---|---|---|---|---|
| FF1 | 298±2.5 | 4.7±0.1 | 4.88 ±0.025 | 0.19 | 99.23 |
| FF2 | 299±0.9 | 5.0±0.02 | 4.62±0.052 | 0.16 | 99.57 |
| FF3 | 297±1.6 | 4.7±0.01 | 4.21±0.005 | 0.17 | 98.06 |
| FF4 | 300±1.5 | 4.8±0.4 | 4.81±0.003 | 0.20 | 98.61 |
| FF5 | 301±2.0 | 4.6±0.01 | 4.56±0.045 | 0.26 | 97.62 |
| FF6 | 301±2.1 | 4.9±0.4 | 4.44±0.067 | 0.24 | 96.03 |
| FF7 | 299±2.3 | 4.7±0.03 | 4.33±0.007 | 0.25 | 99.06 |
| FF8 | 298±1.7 | 4.8±0.4 | 4.23±0.008 | 0.22 | 99.27 |
| FF9 | 297±1.6 | 4.6±0.02 | 4.56±0.054 | 0.30 | 98.62 |
| FF10 | 300±0.9 | 4.7±0.01 | 4.23±0.069 | 0.32 | 97.06 |
| FF11 | 301±2.1 | 4.0±0.63 | 4.78±0.45 | 0.39 | 98.87 |
| FF12 | 299±2.3 | 4.2±0.31 | 4.65±0.052 | 0.40 | 99.06 |
| FF13 | 298±2.6 | 5.6±0.2 | 4.68±0.056 | 0.39 | 99.78 |
| FF14 | 299±1.8 | 5.9±0.69 | 4.75±0.077 | 0.56 | 98.06 |
| FF15 | 301±1.9 | 5.6±0.25 | 4.69±0.0032 | 0.42 | 100.08 |
| FF16 | 300±1.2 | 5.7±0.44 | 4.52±0.003 | 0.45 | 96.03 |
| FF17 | 300±1.6 | 5.6±0.33 | 4.89±0.005 | 0.42 | 97.86 |
| FF18 | 301±3.6 | 5.8±0.36 | 4.69±0.004 | 0.29 | 100.32 |
| FF19 | 301±1.9 | 5.8±0.59 | 4.52±0.008 | 0.26 | 99.86 |
| FF20 | 296±1.7 | 5.9±0.43 | 4.78±0.007 | 0.32 | 99.56 |
| FF21 | 297±1.4 | 5.1±0.77 | 4.23±0.004 | 0.23 | 98.74 |
| FF22 | 298±1.2 | 4.7±0.1 | 4.89±0.006 | 0.25 | 95.35 |
| FF23 | 299±1.2 | 4.9±0.22 | 4.23±0.045 | 0.56 | 97.83 |

| | | | | | |
|---|---|---|---|---|---|
| FF24 | 299±2.0 | 5.4±0.59 | 4.56±0.078 | 0.36 | 98.62 |

***In-Vitro* Drug Release Studies**

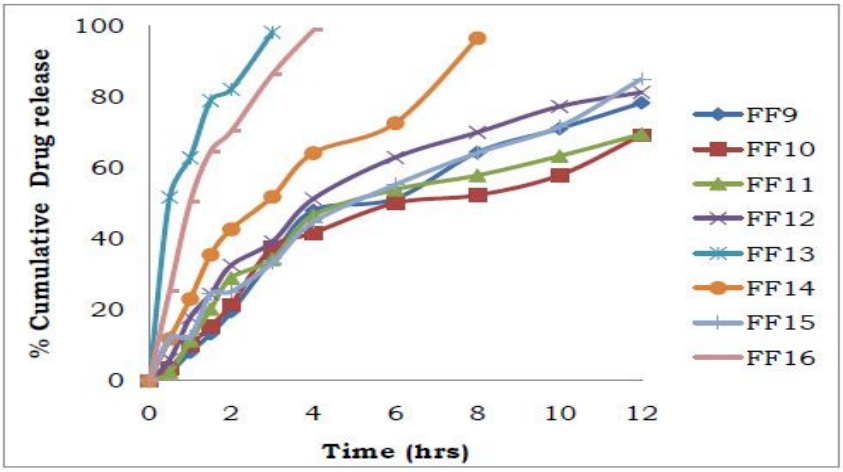
**Figure: 4 Cumulative % Drug release of FF1-FF8**




It was observed that FF1 and FF2 containing 1:0.25 concentration of the lipophilic polymers Gelucire 43/01 and Gelucire 50/02, have shown 94.11% and 96.32% drug release in 3 hrs.FF3 and FF4 containing Geleol and Compritol, with 1:0.25 concentration have shown 89.03% and 94.06% of drug release in 4 hrs. This indicates that 0.25 ratio concentration of any polymer is not sufficient to retard the drug release.

For formulations, FF5 and FF6 containing higher concentration ratios (1: 0.5) of Gelucire 43/01 and Gelucire 50/02, have shown 92.21% and 98.12 % drug release in 6 hrs. FF7 containing Geleol with 1:0.5 concentration has shown 99.71% within 10 hrs, whereas FF8 with Compritol has shown drug release of 96.68 % in 12 hrs, which indicates 0.5 ratio concentration of polymer Compritol 888 ATO is sufficient to retard the drug release.

**Figure: 5 Cumulative % Drug release of FF9-FF16**




For formulations, FF9 and FF10 containing more higher concentration ratios (1: 0.75) of Gelucire 43/01 and Gelucire 50/02, the lipophilic polymers have shown 78.23 % and 69.14 % drug release in 12 hrs.FF11 and FF12, prepared with Geleol and Compritol respectively with 1:0.75 concentration has shown 69.45% and 81.19 % within 12 hrs, which indicates 0.75 ratio concentration of polymer is much more helpful in retardation of the drug release.

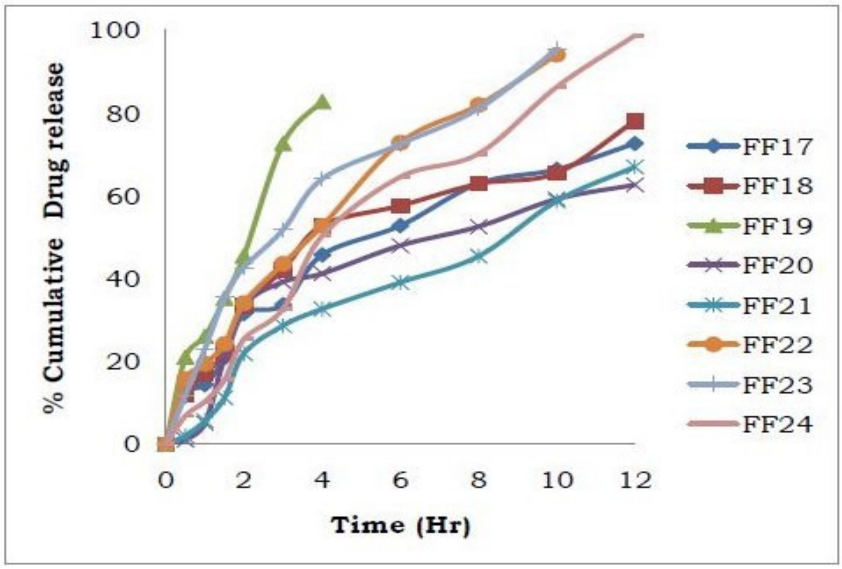
Formulations FF13- FF21 were prepared with hydrophilic polymers like HPMC K15, HPMC K100 and Polyox 303 WSR in different drug to polymer ratios of 1: 0.25, 1:0.5 and1:0.75.

Formulations containing Polyox at three concentration ratios (1: 0.25, 1:0.5 and 1:0.75) i.e., FF13, FF16, FF19 were found to release the drug for 98.14% for 3 hrs, 98.75 % for 4 hrs, 82.87 % for 4 hrs respectively. Even increased concentrations of Polyox there is no much retardation in drug release was observed. Formulations containing HPMC K15 M at three concentration ratios (1: 0.25, 1:0.5 and 1:0.75) i.e., FF14, FF17, FF20 were found to release the drug 96.43% for 8 hrs, 72.68 % for 12 hrs and 62.69 % for 12 hrs respectively.

For HPMC K100 containing formulations, at three concentration ratios (1: 0.25, 1:0.5 and 1:0.75), FF15, FF18, FF21 were found to release the drug 84.98%, 78.07 % and 67.03% for 12hrs respectively.

This indicates that in case of formulations with HPMCs, an increase in concentration of polymer lead to more drug release retardation. By observing the drug release profiles for formulations containing lipophilic and hydrophilic polymers, it was found that lipophilic polymer, Compritol 888 ATO showed more drug retardation properties in comparison to other lipophilic polymers. Whereas, among the hydrophilic polymers, HPMC K100, at 1:0.25 concentration ratio has found with more prominent drug release properties. So, the combination of lipophilic polymer, Compritol 888 ATO and hydrophilic polymer, HPMC K100 were chosen for further studies.

**Figure: 6 Cumulative % Drug release of FF17-FF24**




Therefore, formulations FF22- FF24 were prepared with combination of Compritol 888 ATO and HPMC K100 at different polymer to polymer ratios 1:0.5, 1:1 and 0.5:1

FF22 has shown drug release of 94.14 %, FF3 has shown 95.43 % for 10 hrs and FF4 has shown 98.75 % of drug release for 12 hrs. Among these concentration ratios, 0.5:1 (Compritol 888 ATO: HPMC K100) has shown optimum drug release properties. Thereby, FF24 was chosen as the best optimized formulation for further swelling and buoyancy studies.

**Kinetic modeling of Drug ReleaseProfiles**

In order to establish the drug release mechanism, the *in-vitro* release data was fitted in to exponential forms like Zero order, First order, Higuchi Plot and Korsmeyer- Peppas Equations.

The regression coefficient obtained for zero order kinetics was found to be higher than first order kinetics for all the formulations, indicating that the drug release followed zero order kinetics. To evaluate the drug release mechanism, plots of cumulative percentage drug release vs square root of time as per Higuchi equation and also Korsmeyer-Peppas equation was constructed. These plots were found to be linear and among all the formulations FF24 containing 0.5:1 concentration ratio of Compritol 888 ATO and HPMC K100 was optimized as the best formulation with $R^2$ of 0.970 and n value with 1.083, which indicates the mechanism of drug release was a non-fickian model.

**Table: 9 Release Kinetics data of Optimized formulation (FF24)**

| Parameter | $R^2$ Values | | | | nValue |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Korsmeyer-Peppas | Korsmeyer-Peppas |
| FF24 | 0.970 | 0.830 | 0.962 | 0.984 | 1.083 |

**Figure: 7Zero order plot of formulation FF24**

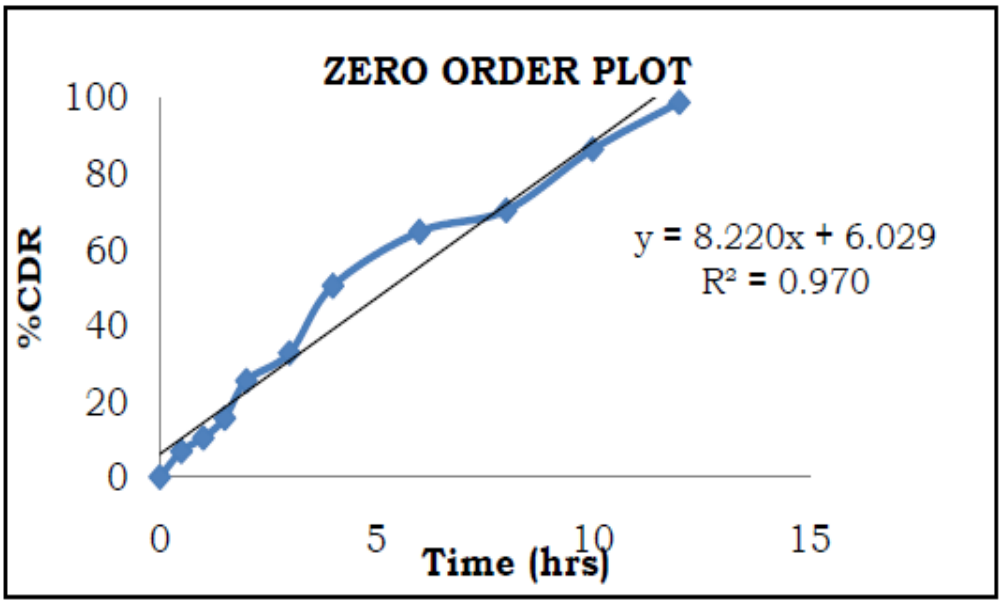


**Figure: 8First order plot of formulation FF24**

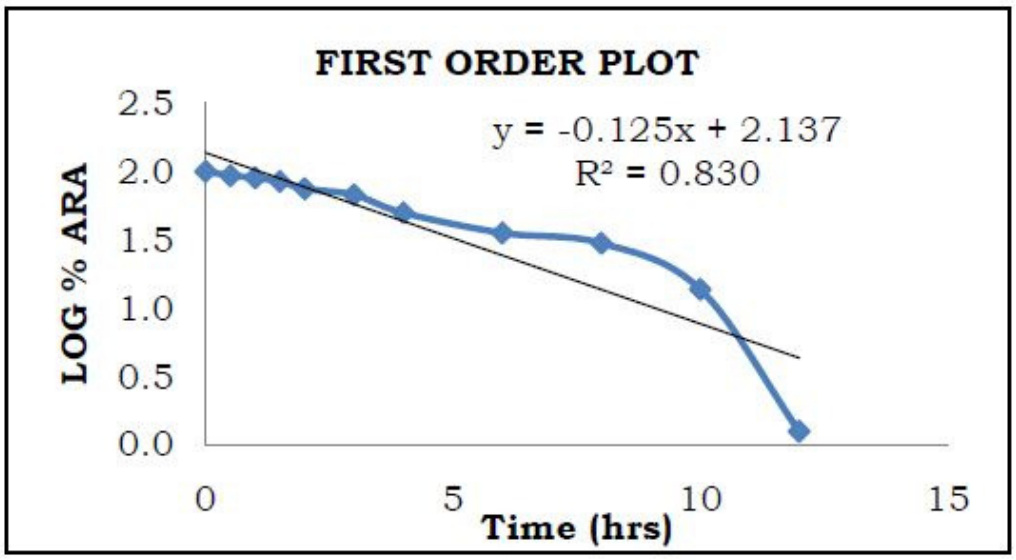



**Figure: 9Higuchi plot of formulation FF24**

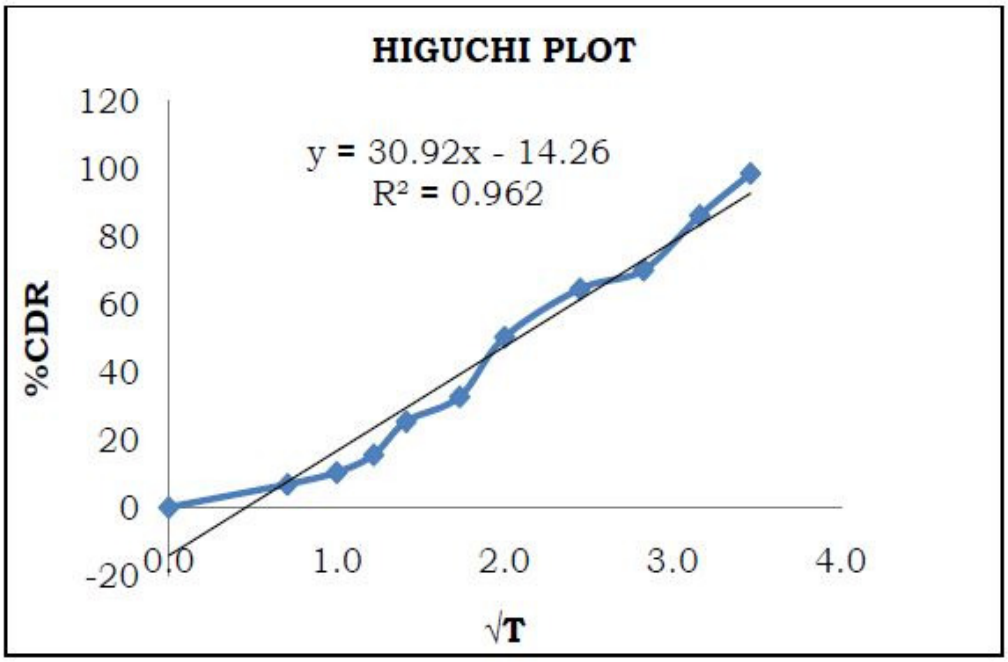
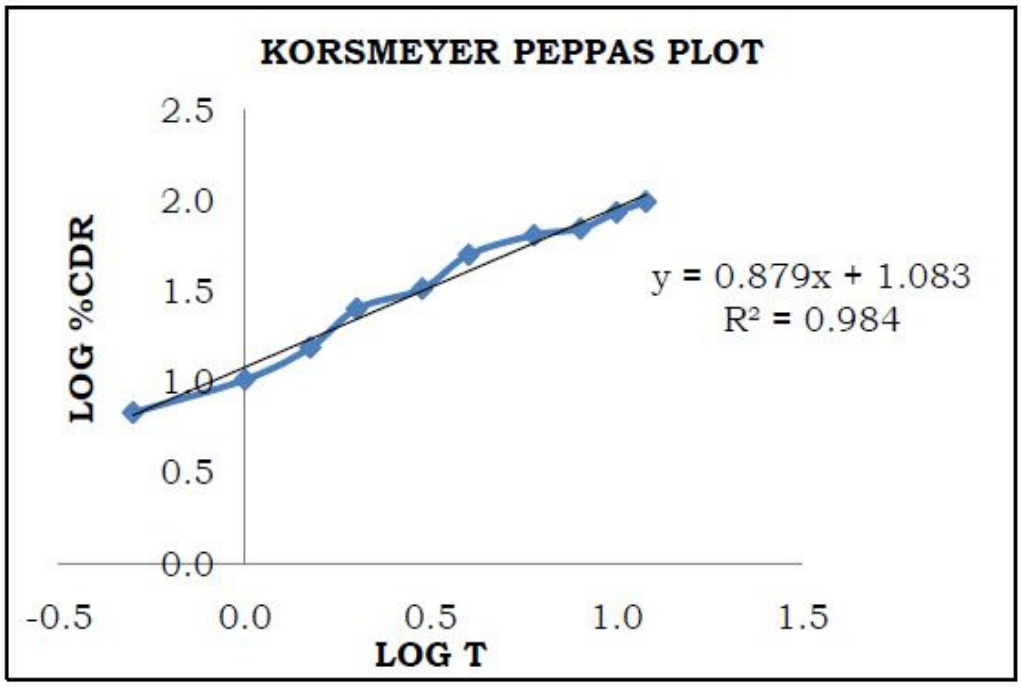


**Figure: 10Korsmeyer-Peppas plot of formulation FF24**




***In- vitro* Swelling Index studies (SI)**

All the formulations were evaluated for degree of swelling. The swelling index was found to increase with the increase in polymer concentration, for all type ofpolymers. Formulations which contain lipophilic polymers were found to possess fewer swelling properties in comparison to the hydrophilic polymers. And among the hydrophilic polymers, formulations containing Polyox has showed less swelling when compared with formulations containing HPMC polymer.

The optimized formulation FF24, has shown more proportional increase in swelling with respect to the concentration of polymer combination, Compritol to HPMC K100 (0.5:1 polymer ratio). Overall results suggest that there is a least but possible effect of swell ability on drug releaseprofile.

**Table :10Swelling index (%)of Famciclovir formulationsFF1-FF18**

| Time (hrs) | FF1 | FF2 | FF3 | FF4 | FF5 | FF6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 12.3±0.35 | 15.4±0.56 | 6.2±0.23 | 16.2±0.25 | 14.2±0.89 | 20.3±0.58 |
| 2 | 20.1±0.26 | 21.4±0.47 | 11.2±0.89 | 23.6±0.66 | 25.4±0.23 | 28.9±0.77 |
| 4 | 25.8±0.14 | 26.4±0.69 | 15.4±0.32 | 32.1±0.23 | 32.1±0.54 | 32.3±0.21 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8 | 34.2±0.25 | 37.1±0.56 | 19.2±0.24 | 51.6±0.45 | 38.3±0.56 | 39.8±0.23 |
| 12 | 40.3±0.27 | 43.6±0.98 | 22.5±0.58 | 62.3±0.85 | 43.5±0.24 | 47.9±0.24 |
| **Time (hrs)** | **FF7** | **FF8** | **FF9** | **FF10** | **FF11** | **FF12** |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 9.3±0.47 | 18.9±0.47 | 24.5±0.47 | 16.2±0.23 | 11.2±0.45 | 21.4±0.65 |
| 2 | 13.5±0.78 | 28.7±0.89 | 32.4±0.56 | 32.7±0.45 | 19.8±0.65 | 31.7±0.23 |
| 4 | 17.8±0.21 | 38.2±0.24 | 39.6±0.23 | 39.5±0.56 | 23.1±0.98 | 51.4±0.57 |
| 8 | 21.4±0.54 | 53.6±0.23 | 45.6±0.47 | 41.3±0.98 | 26.1±0.29 | 61.3±0.69 |
| 12 | 25.9±0.25 | 74.5±0.57 | 49.8±0.54 | 44.7±0.45 | 30.2±0.87 | 79.6±0.78 |
| **Time(hrs)** | **FF13** | **FF14** | **FF15** | **FF16** | **FF17** | **FF18** |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 58.4±0.45 | 48.9±0.58 | 62.8±0.65 | 61.3±0.56 | 49.6±0.51 | 92.4±0.87 |
| 2 | 85.3±0.58 | 79.3±0.48 | 99.6±0.41 | 79.3±0.74 | 79.9±0.45 | 128.4±0.56 |
| 4 | 102.8±0.54 | 109.8±0.78 | 129.9±0.98 | 88.3±0.36 | 111.5±0.35 | 175.2±0.89 |
| 8 | 136.5±0.78 | 142.3±0.45 | 172.1±0.25 | 99.3±0.36 | 137.5±0.69 | 220.5±0.12 |
| 12 | 180.2±0.21 | 178.2±0.23 | 209.3±0.56 | 189.6±0.98 | 189.6±0.45 | 267.2±0.56 |

**Table :11Swelling index (%)of Famciclovir formulationsFF19-FF24**

| **Time (hrs)** | **FF19** | **FF20** | **FF21** | **FF22** | **FF23** | **FF24** |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| 1 | 75.3±0.23 | 59.7±0.56 | 112.7±0.25 | 41.5±0.24 | 41.5±0.78 | **19.6±0.54** |
| 2 | 89.6±0.23 | 87.6±0.56 | 136.3±0.12 | 62.1±0.78 | 56.3±0.47 | **40.9±0.25** |
| 4 | 112.7±0.41 | 122.5±0.23 | 172.1±0.59 | 89.5±0.78 | 74.1±0.89 | **71.2±0.12** |
| 8 | 155.3±0.41 | 155.9±1.05 | 241.2±0.18 | 114.7±0.48 | 87.3±0.45 | **98.5±1.23** |
| 12 | 192.2±1.23 | 195.4±0.58 | 278.7±0.58 | 179.3±0.45 | 128.3±0.58 | **128.3±0.25** |

### *In-vitro* Buoyancy Studies

The *in-vitro* buoyancy studies like floating lag time (FLT) and total floating time duration were performed to assess the gastric ability of Famciclovir gastroretentive tablets, according to the procedure. Results were represented in below the table.

**Table: 12 *In-vitro* buoyancy studies of Famciclovir formulations**

| Parameter | Buoyancy Lag time (Sec) | Floating Duration (Hrs) | Parameter | Buoyancy Lag time (Sec) | Floating Duration (Hrs) |
|---|---|---|---|---|---|
| FF1 | 120 | 2.5 | FF13 | 300 | 3 |
| FF2 | 150 | 3 | FF14 | 120 | 10 |
| FF3 | 120 | 3.2 | FF15 | 120 | 12 |
| FF4 | 120 | 3.3 | FF16 | 300 | 4 |
| FF5 | 150 | 6 | FF17 | 90 | 12 |
| FF6 | 130 | 6.5 | FF18 | 30 | 12 |
| FF7 | 35 | 7 | FF19 | 360 | 4↓ |
| FF8 | 100 | 7.5 | FF20 | 90 | 12 |
| FF9 | 50 | 10 | FF21 | 50 | 12 |
| FF10 | 60 | 10 | FF22 | 150 | 10 |
| FF11 | 45 | 8 | FF23 | 180 | 10 |
| FF12 | 50 | 10 | **FF24** | **30** | **12** |

Lipophilic polymers were found to show less floating duration with more floating lag time. Among all hydrophilic polymer containing formulations, HPMC grades has shown more floating duration with less floating lag time. The formulations containing Polyox were found to get sunk within a short span oftime. Therefore, FF24 is considered as the best optimized formulation which has showed floating lag time of 30 sec with more than 12 hrs of floating duration. It was found to be the best buoyancycharacteristics.

## CONCLUSION

In the present study floating drug delivery formulations of Famciclovir has been successfully designed using various hydrophilic and lipophilic polymers in various concentrations by wet and melt granulation methodswith appropriate pre- and post-formulation studies. It is evident from the results that there is no drug-polymer interaction and FF24 is considered as the best optimized formulation with adequate floating property, non-fickian controlled drug release and followed zero order kinetics.

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