



Development and *In-vitro*, *In-vivo* Evaluation of Gastro Retentive Floating Tablets of Felodipine

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Direct compression was utilized to develop the floating tablets, because of moisture sensitivity of Felodipine(FD), formulation included polymers such as CARBOPOL 934 & HPMC K 15 M. FD Floating tablets were designed to enhance drug availability by prolonging gastric retention time (GRT). Physical properties of tablets, such as hardness, thickness, friability, and weight variation as well as drug content and floating behaviors, were evaluated. Further, tablets were studied for *In vitro* drug release tests for 12 hours, while floating in the dissolution medium, *In- vivo* imaging studies were conducted. According to FTIR studies, there is no interaction between the drug and polymer, *In-vitro* buoyancy of tablets was 12 hours, the *in-vitro* dissolution release studies exhibited sustained and prolonged drug release profiles. The release mechanism from these tablets has been confirmed to be non-Fickian diffusion, which also fits the zero order and Higuchi models, GRT of floating tablets was observed to be 4 hours. Based on *in-vitro* characteristics, F14 is the most efficient formulation. It was exploited *in- vivo* imaging studies by incorporating BaSO₄, and the floating concept was used to boost gastric retention time, which was initially assumed.

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Keywords: Felodipine; floating tablets; gastric retentive drug delivery system; gastric retention time, In- vitro buoyancy.

ABBREVIATIONS USED

FD : Felodipine
 HPMC : Hydroxy Propyl Methyl Cellulose
 GIT : Gastro intestinal Tract
 MCC : Micro Crystalline Cellulose
 HCL : Hydrochloric Acid
 % : Percentage
 Hrs : Hours
 Ml : Milli Liter
 Mg : Milli Grams
 Nm : Nano Meter
 RH : Relative Humidity
 °C : Degree Celcius

1. INTRODUCTION

Oral sustained release dosage systems have been proposed over the last three decades due to its numerous therapeutic benefits. Furthermore, for a lot of significant drugs with a narrow absorption window in the upper gastro intestinal tract (GIT), including stomach and upper small intestine, this strategy is inefficient, this would be owing to the dosage form's shorter transit time through these physiological regions. As a result, whenever the sustained release dosage form has left the upper GIT in a short time, the drug is released in non-absorbing distal segments of the GIT. As a result, there is indeed a rapid absorption phase and lower bioavailability. Several efforts have been made to improve drug absorption following oral administration. Rapid gastro intestinal transit may result in partial drug release, resulting in diminished efficacy of the dose [1,2]. Gastro-retentive drug delivery systems are a perfect example, bio adhesive or mucoadhesive systems, expandable systems, high density systems, floating systems, super porous hydrogels, and magnetic systems are some of the approaches for increasing stomach residence

time [3,4]. They were developed to improve the bioavailability and effectiveness of drugs while promoting local activity in the stomach and/or providing an absorption window in the upper gastro intestinal tract [5,6].

Felodipine (FD) is a calcium channel blocker (CCB) that belongs to the dihydropyridine (DHP) class, which is the most commonly used. FD is an anti hypertensive drug that is administered orally, it is well absorbed from the gastro intestinal tract, and has a small absorption window.

2. MATERIALS AND METHODS

Felodipine was obtained as a gift sample from Micro labs Bangalore, CARBOPOL 934, HPMC K 15M, Micro crystalline cellulose(MCC-Avicel 101), and Sodium bicarbonate, Magnesium stearate, Talc were obtained from S.D fine chemicals Mumbai.

2.1 Formulation of Floating Tablets of Felodipine

Polymer blend strengths, such as CARBOPOL 934 and HPMC K 15 M, have been used in the compositions. Felodipine, stipulated polymers, Micro crystalline cellulose, Sodium bicarbonate, Magnesium stearate, and Talc were accurately weighed, then symmetrically blended for 5 to 10 minutes, then placed in a poly ethylene bag and further mixed for 5 minutes to ensure a homogenous mass, and compressed into tablets using an 8-mm flat surface punch on a 16 station punching machine (Cadmach, Ahmedabad) [7]. Floating tablets were manufactured using drug and different polymer concentration ratios shown in Tables 1 to 2.

Table 1. Formulation of floating of tablets with Carbopol 934

Ingredients	F1	F2	F3	F4	F5	F6	F7
Felodipine	10	10	10	10	10	10	10
Carbopol 934	20	30	60	90	100	110	120
MCC	137	127	97	67	57	47	37
NaHCO ₃	30	30	30	30	30	30	30
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg.Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	200	200	200	200	200	200	200
Weight in (mg)							

Table 2. Formulation of Floating of tablets with HPMC K 15 M

Ingredients	F8	F9	F10	F11	F12	F13	F14
Felodipine	10	10	10	10	10	10	10
HPMC K 15 M	20	30	60	90	100	110	120
MCC	137	127	97	67	57	47	37
NaHCO ₃	30	30	30	30	30	30	30
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg.Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	200	200	200	200	200	200	200
Weight in (mg)							

2.2 Fourier Transforms Infrared Spectroscopy (FTIR)

A SHIMADZU FTIR Spectrophotometer was used to record the infra red spectrum of pure drug, each retardant and physical mixture of the formulation. The KBr disc method used to obtain the samples' IR spectra, and the scanning range was 500-4000 cm⁻¹. To see if there were any chemical reactions, any changes in the drugs' spectrum pattern due to the presence of polymers were analyzed [8].

2.3 Pre- compression Parameters

Angle of repose, bulk density, true density, hausner ratio, and Carrs' index were all performed as per Indian pharmacopeia protocols [9].

2.3.1 Angle of repose

There are several methods for determining the angle of repose, the most common of which is the funnel method. The funnel was filled with a precise amount/weight of grains and powder. The powder or granules to which the flow characteristic must be imparted it was allowed to pass through the funnel (poured) until the very tip. When the powder came into contact with the funnel's tip, the experiment was stopped, and the diameter of the powder heap's base was measured. The formula was used to compute the powders angle of repose.

$$\theta = \tan^{-1} h/r$$

Where, h = height of file

R = radius of the pile's base

θ = angle of repose

2.3.2. Determinations of bulk density and tapped density

The volume (vo) was measured after an accurately weighed quantity of powder (w) was

gently poured into the graduated cylinder. The graduated cylinder was then covered with a lid and placed into the density measurement equipment (Bulk density apparatus) which was set for 500 taps.The volume (vf) was measured and the equipment was kept running until two consecutive readings were obtained.

$$\text{Bulk Density} = W/V_o$$

$$\text{Tapped Density} = W/V_f$$

Where, Vo= Initial volume,

Vf= final volume

2.3.3 Compressibility index and Hausner ratio

The compressibility index and hausner ratio are both measures of a powder's compressibility.As such, they measure the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less significant, and the bulk and tapped densities will closer in value. There are usually greater inter particle interactions in poorer flowing substances, leading to a large difference between bulk and tapped densities. These differences are reflected in the compressibility index and the hausner ratio. By comparing the values for bulk density and tapped density, the compressibility index and hausner ratio can be calculated.

$$\text{Compressibility index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

2.4 Post Compression Parameters

The weight uniformity, hardness(Monsanto tester),thickness(Verniercalipers),friability(Roche friabilator), drug content, in vitro buoyancy, and in vitro dissolution tests of the prepared floating tablets were all assessed, and the results were presented as a mean \pm SD [10,11].

2.5 Floating Properties of Tablets

In- vitro buoyancy was determined by floating lag time and total floating time (TFT).A 100 ml beaker

containing 0.1 N HCl was used for the experiment. The time it took for a tablet to rise to the surface of the dissolution fluid and the total length of time it floated on the dissolution medium were recorded as floating lag time and total time, respectively [12].

2.6 *In-vitro* Dissolution Studies

The USP XXIII dissolution test apparatus was used to determine the FD dissolving profiles in triplicate at $37^{\circ} \pm 5^{\circ}$ c (LAB INDIA, DISSO 2000). The dissolution medium was 900 ml of 0.1 N HCl with a paddle stirring rotating at 50 rpm, at pre determine intervals, samples (5ml) withdrawn and filtered through 0.45 mm pre filter. After being diluted with dissolution media, the absorbance of the filtered samples was determined at 234 nm [13].

2.7 Kinetic Release

The dissolution profile of all batches were fitted to various kinetic models such as zero-order, first-order, Higuchi and Peppas model to assess the kinetic modeling of drug release.

2.7.1 Zero order

$$Q_t = Q_0 + K_0 t$$

Where Q_0 is the initial amount of drug, Q_t is the cumulative amount of drug release at time t , K_0 is the zero order release constant, and t = time in hours represents conditions where the drug release rate is independent of the dissolved substance's concentration [13].

2.7.2 First order

$$\text{Log } Q_t = \text{Log } Q_0 + K_t / 2.303$$

The drug release rate is influenced by its concentration, where Q_0 is the initial amount of drug, Q_t is the cumulative amount of drug release at time t , K is the first order release constant, and t = time in hours [14].

2.7.3 Higuchi equation

$$Q = K H t^{1/2}$$

The drug is released by a diffusion mechanism, according to the Higuchi formula

At time t , Q is the total amount of drug released, KH is the constant, and t is the time in hours

2.7.4 Peppas model

$$M_t/M_{\infty} = K t^n$$

Where M_t and M are the cumulative amounts of drug released at time t and infinite time, respectively, k is a constant which integrates the device's structural geometric properties, and n is the drug release exponent. The R^2 values for the linear curves were calculated. The values for the linear curves obtained from the above plot's regression analysis were determined. The n values were calculated using the slope of the above equation, whereas n values between 0.5 and 1.0 were through to show super position of both processes (anomalous transport) [15].

2.8 *In-vivo* (x-ray) Studies

To conduct this research, 200 mg tablets were prepared were made with BaSO_4 included to make the tablet opaque, the drug dose was replaced with BaSO_4 for *in-vivo* studies and some of the MCC were replaced with BaSO_4 [16].

2.8.1 *In-vivo* buoyancy by using radiographic studies

Human volunteer were assigned FD floating tablets to consume and were observed via radiography technique. After obtaining consent, three healthy male individuals (mean age 26 years, mean weight 60 ± 10 kg) took part, which was carried out by giving each subject one tablet. The floating tablets were given orally with a glass of water, and the individuals were not allowed to eat, but were allowed to drink water as long as they sat or stood upright. X-ray pictures were taken at time intervals of 1 hr, 2hr, and 4 hr [16].

2.9 Stability Studies

Thermo lab TH 90S stability chamber was utilized to maintain the optimized preparation's stability at $40^{\circ} \pm 2/75\%$ RH for three months in compliance with ICH rules, including appearance, weight variation, thickness, hardness, friability, drug content, floating lag time, and total floating time [17].

3. RESULTS AND DISCUSSION

3.1 FTIR (Fourier Transforms Infrared Spectroscopy)

The absence of drug/polymer interaction was developed by FTIR and FTIR spectrum exploration was performed to investigate a physical mixing of drug and polymer for every physical and chemical discrepancy of the drug. Because the primary peaks of Felodipine and HPMC K 15 M were found to be intact. The results of FTIR suggested that there was no interaction in the functional groups, indicating that they were chemically compatible (Fig. 1, 2).

3.2 Pre Compression Parameters

The Hausner ratio was found to be between 1.08 ± 0.05 and 1.22 ± 0.02 , indicating the good flow properties and acceptable, The angle of repose

was found to be between $23.2^{\circ} \pm 0.04$ and $28.3^{\circ} \pm 0.03$, confirming that acceptable as per specification's, the percentage compressibility index was reported to be in the range of 10.43 ± 0.03 to 20.23 ± 0.05 , indicating good compressibility, pre-compression parameters are within specifications as per Indian pharmacopeia and acceptable shown in Table 3.

3.3 Post Compression Parameters

Table 4 summarizes the post-compression parameters, the tablets were of acceptable hardness. The thickness of all formulations ranged from 3.08 ± 0.02 to 3.69 ± 0.06 mm, a weight variation of 199 ± 0.01 to 201 ± 0.02 mg, and a drug content ranging from 97.1 ± 0.02 to 99.7 ± 0.03 . Friability was less than 0.5 percent for all formulations, post-compression parameters are also within in range, and having strong mechanical strength.

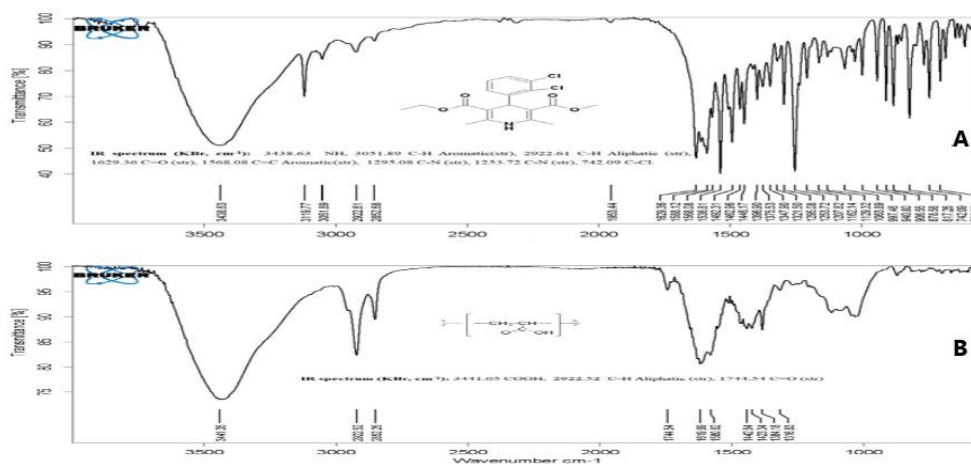


Fig. 1. A) FTIR Spectra of Pure Felodipine, B) FTIR Spectra of Carbopol 934

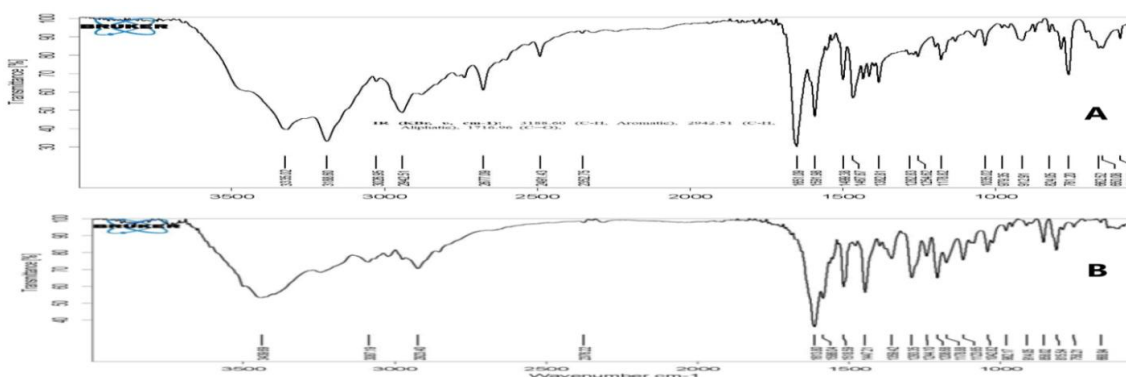


Fig. 2. A) FTIR Spectra of Optimized formulation (F14), B) FTIR Spectra of HPMC k 15 m

Table 3. Pre compression parameters

Formulations Code	Angle of repose	Bulk Density(gm/cm) ³	Tapped Density(gm/cm) ³	Carrs Index(%)	Hausner Ratio
F1	23.2±0.04	0.53±0.01	0.66±0.04	19.34±0.04	1.22±0.12
F2	24.1±0.05	0.55±0.03	0.67±0.06	17.23±0.06	1.21±0.08
F3	25.6±0.04	0.56±0.05	0.64±0.05	15.34±0.03	1.14±0.04
F4	26.7±0.05	0.57±0.04	0.65±0.02	11.32±0.05	1.14±0.07
F5	28.3±0.03	0.56±0.07	0.70±0.05	20.34±0.06	1.20±0.06
F6	25.6±0.04	0.55±0.02	0.67±0.03	17.91±0.02	1.21±0.05
F7	25.5±0.06	0.54±0.03	0.68±0.04	20.34±0.06	1.22±0.02
F8	27.0±0.03	0.54±0.06	0.66±0.03	18.03±0.06	1.18±0.04
F9	26.1±0.01	0.52±0.05	0.64±0.08	18.56±0.03	1.19±0.02
F10	25.0±0.04	0.53±0.02	0.65±0.06	18.50±0.06	1.20±0.04
F11	26.5±0.06	0.58±0.04	0.68±0.08	14.53±0.05	1.19±0.06
F12	27.0±0.04	0.59± 0.02	0.66 ± 0.07	10.54±0.08	1.15±0.03
F13	27.5± 0.05	0.57± 0.01	0.67 ± 0.05	14.21±0.04	1.16±0.08
F14	23.3± 0.03	0.58± 0.07	0.69± 0.03	15.23±0.06	1.08±0.05

Table 4. Post compression parameters

Formulation code	Hardness (kg/cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)	Total Floating Time (hrs)	Floating Lag Time (sec)	Weight Variation (%)
F1	3.5 ±0.07	0.28±0.02	3.09±0.03	99.1±0.02	6 hrs	56 sec	199±0.01
F2	3.8±0.03	0.27±0.01	3.10±0.01	97.5±0.04	7 hrs	55 sec	200±0.02
F3	3.9±0.06	0.30±0.03	3.08±0.02	98.2±0.02	7 hrs	53 sec	199±0.04
F4	4.2 ±0.06	0.42±0.02	3.15±0.03	98.6±0.01	7.5 hrs	50 sec	200±0.03
F5	4.1±0.07	0.49±0.01	3.26±0.01	97.1±0.02	9 hrs	48 sec	200±0.05
F6	3.5±0.09	0.3±0.01	3.31±0.02	99.7±0.03	9.5 hrs	45sec	199±0.08
F7	3.7±0.06	0.29±0.02	3.51±0.01	98.4±0.04	11 hrs	42 sec	200±0.07
F8	3.6 ±0.02	0.30±0.04	3.09±0.08	98.6±0.06	6.0hrs	51 sec	199±0.05
F9	3.7±0.04	0.31±0.07	3.10±0.02	98.4±0.02	6.5 hrs	48sec	201±0.02
F10	3.8±0.09	0.32±0.08	3.14±0.05	97.9±0.07	7 hrs	45sec	200±0.08
F11	4.0±0.09	0.42±0.03	3.24±0.06	98.5±0.06	7.5 hrs	43 sec	199±0.04
F12	4.2±0.01	0.41±0.03	3.26±0.06	97.6±0.07	10 hrs	41sec	200±0.07
F13	4.1±0.07	0.39±0.04	3.41±0.05	99.2±0.01	11hrs	40sec	199±0.02
F14	3.9±0.06	0.30±0.03	3.69±0.06	99.6±0.03	12 hrs	38 sec	200±0.05

n=3 ± mean

3.4 Floating Properties of Tablets

After an assessment of all formulations, it was determined that buoyant lag times ranging from 38 to 56 seconds had excellent floating capabilities. Table 4 and Fig. 3 shows the results. Upon addition of sodium bi carbonate rapid floating starts reaction immediately with the acidic dissolution media, which generates sufficient amount of CO₂ which get entrapped and protected within the gel layer formed by hydration of HPMC K 15 M. As a result, the tablets' density reduces (reported as 1.004 to 1.010 g/cm³) and the tablet becomes buoyant. due to its low hydrophilic polymer concentrations total floating time (TFT) of some formulations

were less, and the TFT of optimized formulation (F14) was reported to be 12 hours.

3.5 In-vitro Dissolution Studies

The release of FD from different formulations depending on the characteristics and mix of matrix forming polymers. The *in-vitro* profile of F1-F7 and F8-F14 formulations shown in Figs. 4, 5. F1, F2 and F8, F9 were displayed a burst release pattern in the first several hours, which is due to the low amount of polymer while increasing the concentration indicated sustained release. The rate and extent of drug release was inversely proportion to the thickness of the hydrogel layer because drug molecules took

longer to travel across the gel layer and reach the dissolution media. The floating tablet's greater polymer concentration allows for the formation of a hydrogel layer, which delays drug release. HPMC K15 M shown a more sustained release profile because which remains un ionized

in acidic dissolution media and leads to act as a physical barrier for sustained release, HPMC K15 M (F14) was shown higher sustained release profile than the CARBOPOL 934 and commercialized formulation in 12 hours.

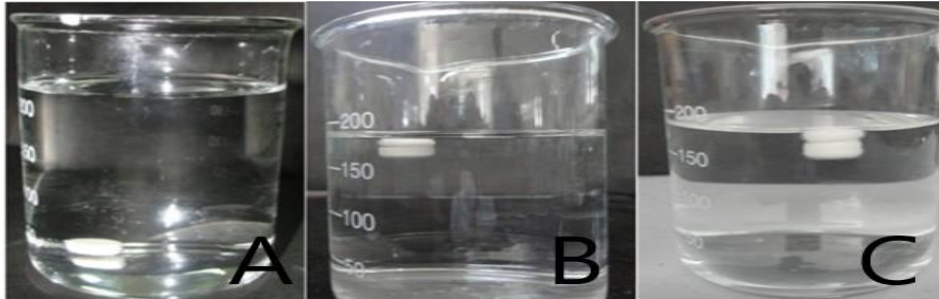


Fig. 3. *In-vitro* buoyancy studies, A) Initial time, B) After 6 hours, C) After 12 h

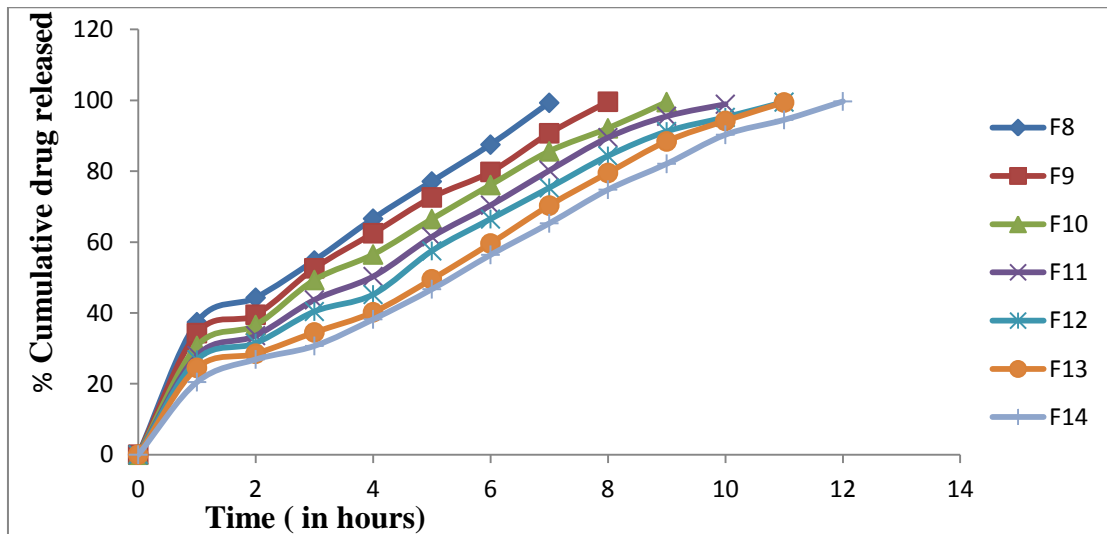


Fig. 4. *In-vitro* dissolution profile of F8-F14 formulation

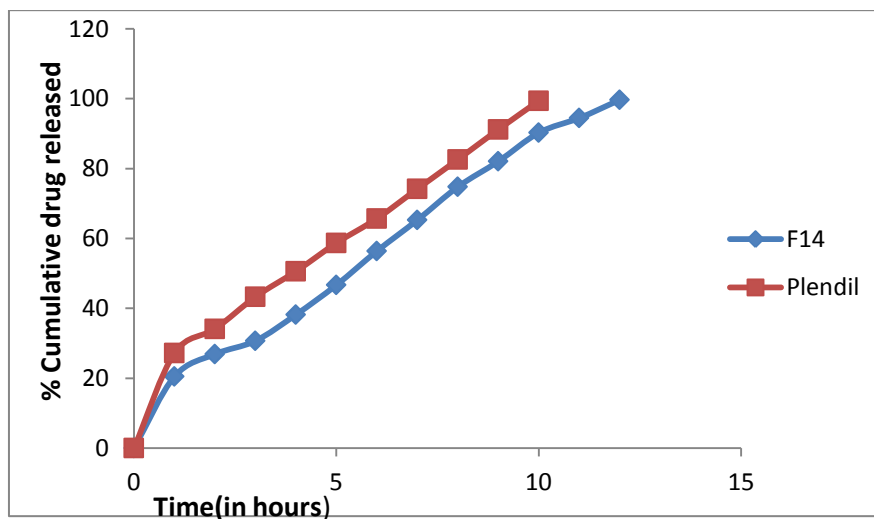


Fig. 5. *In-vitro* dissolution profile of F14 formulation and Plendil (Marketed product)



Fig. 6. *In- vivo* x-ray studies, A) After 1 hour, B) After 2 hours, C) After 4 hours

Table 5. Drug release mechanism

Formulation code	Zero order R ²	First order R ²	Higuchi's R ²	Korsmeyer & Peppas R ²	n
F-1	0.869	0.712	0.934	0.913	0.52
F-2	0.872	0.723	0.942	0.956	0.49
F-3	0.892	0.808	0.945	0.958	0.54
F-4	0.940	0.811	0.957	0.962	0.62
F-5	0.934	0.825	0.950	0.972	0.53
F-6	0.962	0.802	0.962	0.961	0.64
F-7	0.973	0.835	0.968	0.968	0.50
F-8	0.938	0.815	0.952	0.956	0.53
F-9	0.942	0.824	0.948	0.962	0.62
F-10	0.952	0.823	0.950	0.958	0.53
F-11	0.960	0.832	0.960	0.969	0.65
F-12	0.934	0.810	0.961	0.964	0.68
F-13	0.941	0.755	0.957	0.970	0.53
F-14	0.991	0.825	0.970	0.975	0.51

3.6 *In-vivo* X-Ray Studies

The tablets were seen using a radiographic imaging technique, and the tablets were spotted in the stomach (Fig. 6A). The tablet's position had profoundly altered on the following images, taken at 1, 2, and 4 hours, *in-vivo* studies revealed the tablet was in a different spots. The tablets floated on the gastro intestinal fluid rather than adhering to the mucosa, as this revealed (Fig. 6B, C).

3.7 Drug release Mechanism

The release mechanism for FD floating tablets was determined to be diffusion, i.e. non-fickian /anomalous transport, with n values ranging from 0.49 to 0.68 for all preparations. Drug release kinetics followed a zero order profile and peppas's model, and the high regression value of Higuchi model indicated that drug release from matrix tablets followed a diffusion mechanism, F7 ,and F14 formulations shown highest R² values which is because of water diffusion and polymer rearrangements also occurs ,as shown in Table 5.

3.8 Stability Studies

Stability test has been carried out for an optimized formulation in accordance with ICH criteria. The tests lasted three months, and there were no substantial changes in variables like drug content, floating lag time, floating time, hardness, friability, thickness, weight variation.

4. CONCLUSION

Systemic researches have been performed employing two polymers at diverse concentrations to develop FD floating tablets. The optimized formulation (F14) with HPMC K 15 M floated for 12 hours with a log time of 38 seconds, dissolution studies revealed that optimized formulation sustained release for 12 hours longer than marketed product and CARBOPOL 934 formulations, and *in- vivo* radiographic studies revealed that F14 formulation stayed in stomach for 4 hours, revealing that the floating principle enhanced GRT, which was considered.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, respondents' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Approved by human ethical committee of St 'Peters Institute of Pharmaceutical Sciences, Warangal.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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