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Formulation and In-vitro Characterization of Fluoxetine Hydrochloride Loaded Fast Dissolving Oral Film Using HPMC 15CPS and HPMC K4M

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Abstract

Fluoxetine Hydrochloride (FH), a selective serotonin reuptake inhibitor (SSRI) is a drug of choice in depression, obsessive-compulsive disorder (OCD), bulimia nervosa, etc. Though tablet, capsules, oral solution, or syrup are currently available conventional dosage form of FH, modified or immediate-release formulations for fast onset of action is of utmost importance. Therefore, this study was designed to form a fast-dissolving oral film (FDOF) of FH with the use of two film-forming agents HPMC 15CPS and HPMC K4M. The solvent casting method was employed for the formulation of film since the heat required for the evaporation of the solvent is minimum as compared to hot-melt extrusion. Nine different formulations were prepared with the change in polymer and super disintegrant (SSD) concentration. The results revealed that films prepared by both the polymers have acceptable organoleptic properties, neutral pH, and appropriate folding endurance. The result revealed that the film containing high polymer concentration has a greater thickness as compared to the lower concentration. The moisture content value was found to be uniform in all the formulations prepared by both the polymers which lie in the acceptable range of 1.4 to 3.2%. The disintegration time of formulations prepared by HPMC 15CPS and HPMC K4M was found to be in the range of 10 to 33 sec and 1 to 3 minutes, respectively. In the formulation prepared by HPMC 15CPS, the maximum release of drug was occurred at around 3 minutes while in another formulation prepared by HPMC K4M the highest percentage of drug release was 99.23 % for F3 at around 6 minutes. With this formulation and in-vitro characterization, the study paved a footstep for the development of FDOF of FH. Further, an in-vitro and in-vivo pharmacokinetic and therapeutic study of the prepared film will ease to authenticate the efficacy and bioavailability of the FDOF of FH.

Keywords: Fluoxetine Hydrochloride; Fast-Dissolving Oral Film; Solvent Casting Method; HPMC 15CPS; HPMC K4M

List of abbreviations: FH: Fluoxetine Hydrochloride; FDOF: Fast Dissolving Oral Film; HPMC: Hydroxypropyl Methyl Cellulose; OCD: Obsessive-Compulsive Disorder; SSD: Super Disintegrants; PMDD: Premenstrual Dysphoric Disorder; MDD: Major Depressive Disorder; BMI: Body Mass Index; SSRI: Selective Serotonin Reuptake Inhibitor; PG: Polyethylene Glycol; FTIR: Fourier Transform Infrared Spectroscopy; SEM: Scanning Electron Microscopy; Pvt: Private; Ltd: Limited; R^2: Regression Coefficient; SD: Standard Deviation; pH: Potential of Hydrogen

Introduction

Fluoxetine hydrochloride (FH), chemically known as (3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropanolamine HCl was firstly mentioned in scientific journals in 1974 as selective serotonin (5-hydroxytryptamine or 5-HT)-reuptake inhibitor (SSRI) [1]. After the approval by US FDA on 29th December 1987, FH was registered as an early member of a new class of antidepressant drugs [2]. Capsules, tablets, and oral solutions of FH are being used for the treatment of various sorts of ailments such as depression, obsessive-compulsive disorder (OCD), bulimia nervosa, premenstrual dysphoric disorder (PMDD), major depressive disorder (MDD), etc. [3]. The consumption dose of the medicament get varies as per the pathological condition, age, and body mass index (BMI). For reference, the usual adult dose in immediate-release oral formulations to subdue depression is 20 mg orally once a day in the morning as an initial dose. This is followed by the maintenance dose of 20 to 60 mg orally per day being the total sum of 80 mg orally per day. However, in delayed-release oral capsules, the initial dose consumed to overcome depression is 90 mg orally once a week [4]. Though FH is being taken as a common drug of choice for unipolar and bipolar depression, the conventional dosage form of FH is still crowned with several side effects such as alteration in sleeping habits, flu symptoms, sexual problems, loss of appetite, sinus infection, or sore throat, etc. [5]. Meanwhile, depressive disorders are the complication which requires rapid onset of action of the drug along with the sustained delivery of drug for a long time [6]. Therefore, to subside the side effects as well as to meet the patient compliance, a novel approach for the formulation of the dosage form with different release rates and pharmacokinetics such as fast dissolving oral film is of utmost importance.

Fast dissolving oral film (FDOF) which has a historical background since 1970 is a novel approach developed as an alternative to capsules, tablets, and syrups for patients who have difficulties in swallowing and chewing [7]. Due to the rapid onset of action which is required in a sudden episode of allergic attack, coughing, motion sickness, bronchitis, asthma, depression, etc., FDOF is gaining interest nowadays in formulation design and development [8]. FDOF is an ultrathin film prepared using hydrophilic polymers that rapidly dissolves on the top or floor of the tongue or buccal cavity having a surface area of almost 2-8 cm^2 and ideal thickness is between 20-250 μM [9]. Major superiority of FDOF over conventional dosage forms are pediatrics, geriatrics, and psychiatric patient-friendly, lessen the risk of choking and suffocation as well as dosing accuracy in comparison to syrup [10,11]. Consecutively, extensive metabolism caused by proteolytic enzymes could be possibly diminished and rapid onset of action could be acquired with the aid of FDOF [12]. Despite that, there are few points to consider during the formulation of FDOF. They are pH sensitive and drugs showing instability in buccal pH should be withdrawn. Difficulty in the incorporation of high dose and technical challenge in dosing uniformity are a few other points to be noted during design and manufacture [13].

Generally, FDOF is formulated with the incorporation of the drug in film-forming polymer along with plasticizers, flavoring and sweetening agents, surfactant, thickener, stabilizers as well as saliva stimulating agents [14]. Film-forming agents usually employed are made up of cellulose derivative polymer and the change in amount and type of these polymers affects the pharmacokinetics of FDOF to a great extend [15]. On the other hand, manufacturing methods of FDOF even exhibit a rigorous difference in the outcome of drug release and efficacy profile. Generally employed methods for the formulation of FDOF are solvent casting method, hot-melt extrusion technique, semisolid casting method, rolling method, and solid dispersion extrusion method [16]. The solvent casting method was employed in this study for the formulation of oral films of FH. This method is usually employed for the manufacture of films containing heat-sensitive APIs because the temperature required to remove the solvents is relatively low as compared to the hot-melt extrusion method. However, care should be taken to steer clear of trace amount of residual solvents which could present issue in compendial compliance [17].

Meanwhile, successful formulation of solid, liquid, semisolid, as well as modified release dosage forms, are substantially affected by the selection of polymers. Thermoplastics, elastomers, and synthetic fibers are usual synthetic polymers while natural polymers are also gaining interest in the design of numerous drug delivery systems. Two synthetic polymers employed in this study as film-forming agents are Hydroxypropyl Methylcellulose 15CPS (HPMC 15CPS) and Hydroxypropyl methylcellulose K4M (HPMC K4M). HPMC 15CPS denotes that the viscosity of HPMC is 150,000 while HPMC K4M denotes that the viscosity of polymer lies in the medium range of 2700 to 5040 cps and particle size of 170 to 250 micrometers [18,19]. In this study, nine different oral films were prepared for each of the polymers used by altering the concentration of polymer and other excipients taken. Followingly, the in-vitro characterization of the films was performed with the application of standard test methods.

Materials and Methods

Chemicals and Reagents

The experimental drug, Fluoxetine hydrochloride (FH) was obtained as a generous gift from Asian Pharmaceuticals Pvt. Ltd., Bhairahawa, Nepal. Polymers used in the study, HPMCK4M and HPMC 15CPS were obtained as a bounteous gift from Asian Pharmaceutical Pvt. Ltd., Bhairahawa, Nepal, and Times Pharmaceutical Pvt. Ltd., Nawalparasi Nepal. Mannitol used as a sweetener in the study was procured from Thermo Fisher Scientific India Pvt. Ltd., India. propylene glycol and potassium dihydrogen phosphate used were purchased from Fine chemicals, India. Similarly, citric acid and disodium hydrogen phosphate were procured from Organo Laboratories, and Merck Specialties Pvt. Ltd., India respectively. All reagents and chemicals used were of analytical reagent grade.

Formulation of FDOF

FDOF was prepared by solvent casting method given by Deepthi et al, 2014 with the implementation of the factorial design method as mentioned in Table 1 [20]. In the factorial design method, the concentration of super disintegrant (SSG) and polymer i.e., HPMC 15 CPS and HPMC K4M were changed. Concentration of SSG used was 6% (F1, F4, and F7), 8% (F2, F5 and F8) and 10% (F3, F6 and F9). The concentration of polymer used was 35% (F1, F2, and F3), 40% (F4, F5, and F6), and 45% (F7, F8, and F9).

A polymer solution of two different polymers, HPMC 15CPS and HPMC K4M were prepared by dissolving both polymers separately in 5 mL of distilled water and left for 10 minutes in a magnetic stirrer. Drugs and other ingredients were dissolved separately in 5 mL of distilled water and added to the polymer solution. The final solution was mixed in a magnetic stirrer for 1 hour. Deaeration of the solution was done by leaving it overnight and subsequently cast in a petri dish. So obtained solution was kept in a hot air oven at 40 °C until dried. The prepared film was carefully removed, and further studies were performed.

Formulations	API (g)	HPMC (g)	PG (g)	SSD (g)	Citric acid (g)	Mannitol (g)
F1	0.08	0.28	0.22	0.05	0.04	0.06
F2	0.08	0.28	0.22	0.06	0.04	0.06
F3	0.08	0.28	0.22	0.08	0.04	0.06
F4	0.08	0.32	0.22	0.05	0.04	0.06
F5	0.08	0.32	0.22	0.06	0.04	0.06
F6	0.08	0.32	0.22	0.08	0.04	0.06
F7	0.08	0.36	0.22	0.05	0.04	0.06
F8	0.08	0.36	0.22	0.06	0.04	0.06
F9	0.08	0.36	0.22	0.08	0.04	0.06

Where PG = polyethylene glycol and SSD = super disintegrants

Table 1: Amount of ingredients used in the different formulation as per the factorial design method

Physical characterization and In-vitro Pharmacokinetics study

Visual inspection

Homogeneity, transparency, integrity, and color of the produced film were inspected visually as per the method mentioned by Iman Sabah Jaafar et al, 2017 [21].

Weight variation and thickness of the film

Weight variation tests of prepared fast dissolving films were examined as per the method given by Hussain et al, 2017. Each film was cut into four pieces of 14 cm^2 dimensions from every formulated film. The weighing was performed individually on a microgram digital weighing meter and the average weight was calculated.

Followingly, the thickness of each strip was measured at five different locations using calibrated digital Vernier caliper following the method given by Bala et al, 2013 [22]. The experiments were repeated three times.

Surface pH and folding endurance

The surface pH and folding endurance were tested according to the method given by Tomar et al, 2012 [23]. For pH measurement, the testing film was placed in a petri dish, moistened with 0.5 ml distilled water, and kept for 1 hour. The pH was noted using calibrated pH meter in which the bulb of the Ph meter was completely in contact with the surface of the formulation.

For the determination of folding endurance, the films were repeatedly folded at the same place till they broke. The value of folding endurance was achieved from the number of times the film could be folded at the same place without breaking or cracking. The experiments were performed three times.

Moisture content

Moisture content in FDOF was determined as per the method given by Tomar et al, 2012 [23]. The testing film was placed in desiccators filled with activated silica. After three days, the film was taken and reweighed. The same procedure was repeated three times for the verification of the result. The percentage moisture content was calculated using the following formula:

Moisture content % = $\frac{Wo-Wt}{Wo} * 100$

Where,

Wo = Initial weight and Wt = Final weight

Disintegration time

The disintegration time of prepared films was studied following the drop method given by Pries et al, 2012. One film was placed onto a small glass beaker and 0.2 ml (one drop) of distilled water was placed onto the film. The time required for the film to break was noted. The procedure was repeated three times.

Drug content

The drug content in the film was measured following the procedure given by Koland et al, 2010 [24]. The test was performed by dissolving 14 cm^2 area of film in 100 ml of Phosphate buffer of pH 6.8 with continuous stirring for 30 minutes. The resulting solution was filtered using Whatman filter paper and the 10 ml filtrate was diluted to 100 ml with the same buffer in a volumetric flask. The solution was analyzed using a spectrophotometer at a wavelength of 226 nm. The procedure was repeated three times.

In vitro drug release study

The in vitro drug release study of the film was carried out using a USP type 2 dissolution test apparatus similar to the method given by Sultana et al, 2013 [25]. 250ml of phosphate buffer (pH 6.8) was maintained at 37±5 °C and the basket was set at 50 rpm. A film sample of 6 cm^2 (3 cm×2 cm) was fixed onto the specially designed SS disk with the help of cyanoacrylate adhesive. Five milliliters of samples were taken at an interval of 60 sec and the same amount was replaced with fresh buffer. The withdrawn samples were filtered through Whatman filter paper and then 1ml of the filtered sample was further diluted to 25ml of the same medium and analyzed using a spectrophotometer at a wavelength of 226 nm. The cumulative percentage release for different formulations was calculated. The experiment was repeated three times.

Results

Physical Appearance of the film

The film prepared by using both polymers i.e., HPMC 15CPS and HPMC K4M were clear, transparent, odorless, smooth, and flexible as shown in Figures 1 and 2.

Figure 1: Fast dissolving oral films (FDOF) of different formulations (F1 to F9) using HPMC 15CPS as polymer

Figure 2: Fast dissolving oral films (FDOF) of different formulations (F1 to F9) using HPMC K4M as polymer

In-vitro Characterization study

Weight variation

The weight of films measured by using digital analytical balance is given in Table 2. The weight of films prepared by using HPMC 15CPS and HPMC K4M varies from 0.1512±0.034 to 0.2050±0.026 g and 0.1403±0.003 to 0.1681±0.002 g respectively.

Formulations	Weight Variation (g)	
	HPMC 15cps	HPMC K4M
F1	0.1548±0.037	0.1681±0.002
F2	0.01569±0.004	0.1634±0.008
F3	0.1581±0.030	0.1458±0.012
F4	0.1595±0.023	0.1403±0.003
F5	0.1512±0.034	0.1494±0.003
F6	0.1462±0.016	0.1488±0.006
F7	0.1671±0.029	0.1556±0.007
F8	0.2050±0.026	0.1662±0.013
F9	0.1588±0.035	0.1613±-0.024

Data are expressed as mean ± standard deviation (n=3)

Table 2: Weight Variation of films prepared by using HPMC 15 CPS and HPMC K4M

Thickness

The thickness of the films which was determined by using Vernier Caliper at three different points of the film is shown in Table 3. The result revealed that the film containing high polymer concentration has a greater thickness as compared to the lower concentration.

Formulation	Thickness (mm)	
	HPMC 15cps	HPMC K4M
F1	0.1442±0.037	0.1561±0.002
F2	0.1457±0.004	0.1434±0.008
F3	0.1433±0.030	0.1458±0.012
F4	0.1489±0.023	0.1657±0.003
F5	0.1512±0.034	0.1601±0.003
F6	0.1498±0.016	0.1568±0.006
F7	0.1671±0.029	0.1701±0.007
F8	0.1688±0.026	0.1769±0.013
F9	0.1673±0.035	0.1688±-0.024

Data are expressed as mean ± standard deviation (n=3)

Table 3: Thickness of different films prepared using HPMC 15CPS and HPMC K4M

Surface pH

The surface pH of films prepared with the use of polymer HPMC 15CPS and HPMC K4M was determined which is shown in Figure 3. The pH lied in the neutral pH range from 6.7 to 7.1.

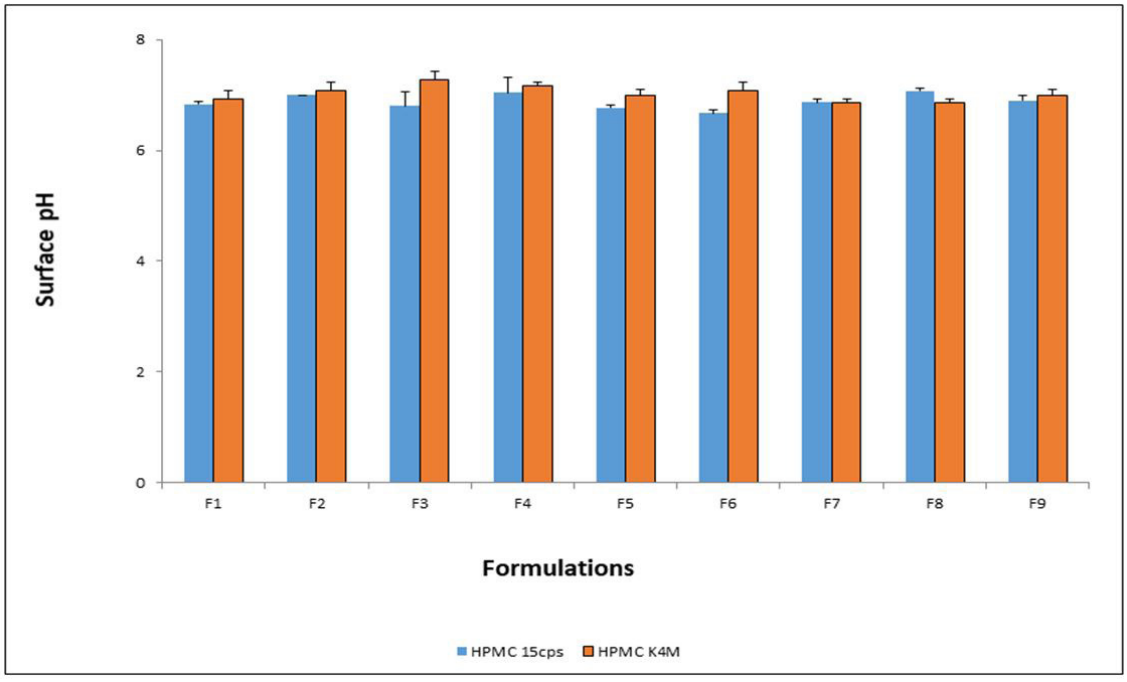

Figure 3: Surface pH of formulations prepared by using HPMC 15CPS and HPMC K4M

Folding endurance

The folding endurance of all the formulations prepared is shown in Table 4. The result demonstrated that the folding endurance of all the formulations was found to be greater than 150.

Formulation	Folding Endurance	
	HPMC 15cps	HPMC K4M
F1	>150	>150
F2	>150	>150
F3	>150	>150
F4	>150	>150
F5	>150	>150
F6	>150	>150
F7	>150	>150
F8	>150	>150
F9	>150	>150

The experiment was repeated three times (n=3) and the result obtained was similar in all experiments.

Table 4: Folding endurance of films prepared by using HPMC 15CPS and HPMC K4M

Moisture content

The moisture content of all the formulations prepared by HPMC 15CPS and HPMC K4M was determined which was shown in Table 5. The moisture content value was found to be uniform in all the formulations prepared by both the polymers which lie in the acceptable range of 1.4 to 3.2%.

Formulations	Moisture Content (%)	
	HPMC 15cps	HPMC K4M
F1	2.166±0.440	2.287±0.342
F2	1.680±0.708	2.480±0.439
F3	2.175±0.396	2.977±0.555
F4	1.332±0.195	2.785±0.244
F5	1.942±0.241	3.240±0.310
F6	2.882±0.770	3.196±0.116
F7	2.409±0.868	2.063±0.326
F8	1.761±0.777	2.635±0.367
F9	1.468±0.577	2.899±0.622

Data are expressed as mean ± standard deviation (n=3)

Table 5: Moisture content of films prepared by using HPMC 15CPS and HPMC K4M

Disintegration Time

The disintegration time of all the formulations is shown in Figure 4. The disintegration time of formulations prepared by HPMC 15CPS and HPMC K4M was found to be in the range of 10 to 33 sec and 1 to 3 minutes, respectively. Results revealed that the concentration of super disintegrant is inversely related to the disintegration time.

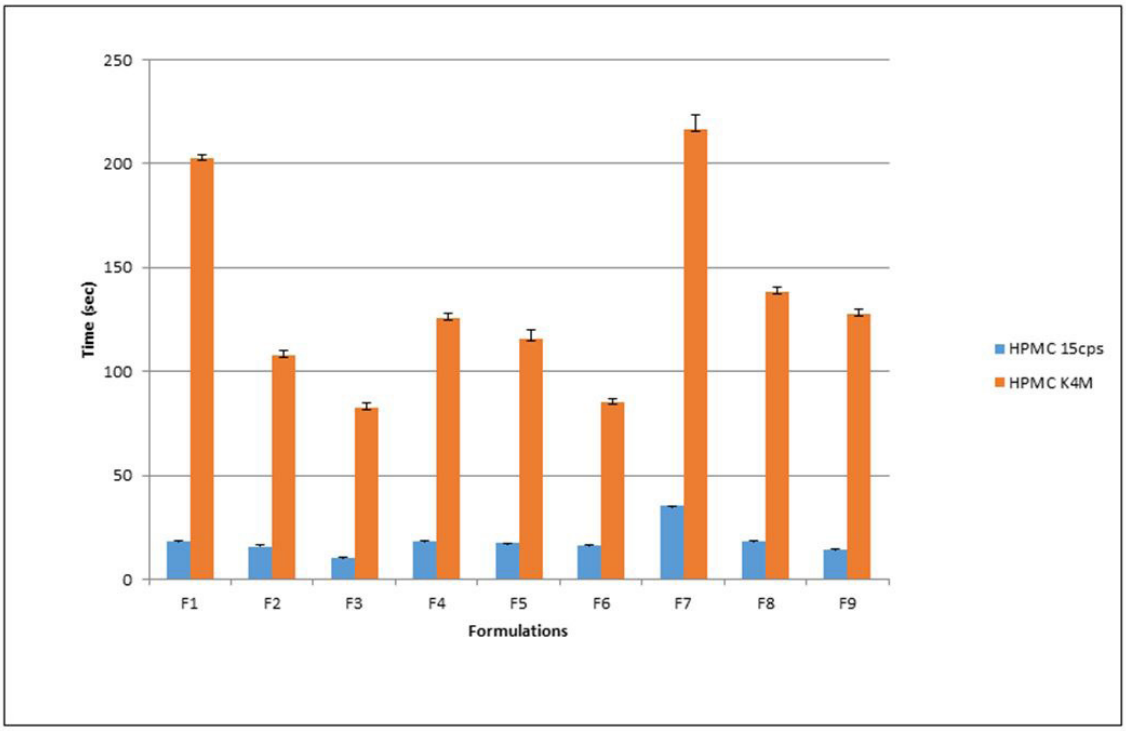

Figure 4: Disintegration time of films prepared by using HPMC 15CPS and HPMC K4M

Drug Content

For the determination of drug content calibration curve of Fluoxetine Hydrochloride was drawn by plotting absorbance versus concentration (mcg/ml) as shown in Figure 5. The line obtained was found to be linear with regression coefficient R^2 =0.9984 showing it adheres with Beer's Law.

The percentage drug content of the prepared films is shown in Table 6.

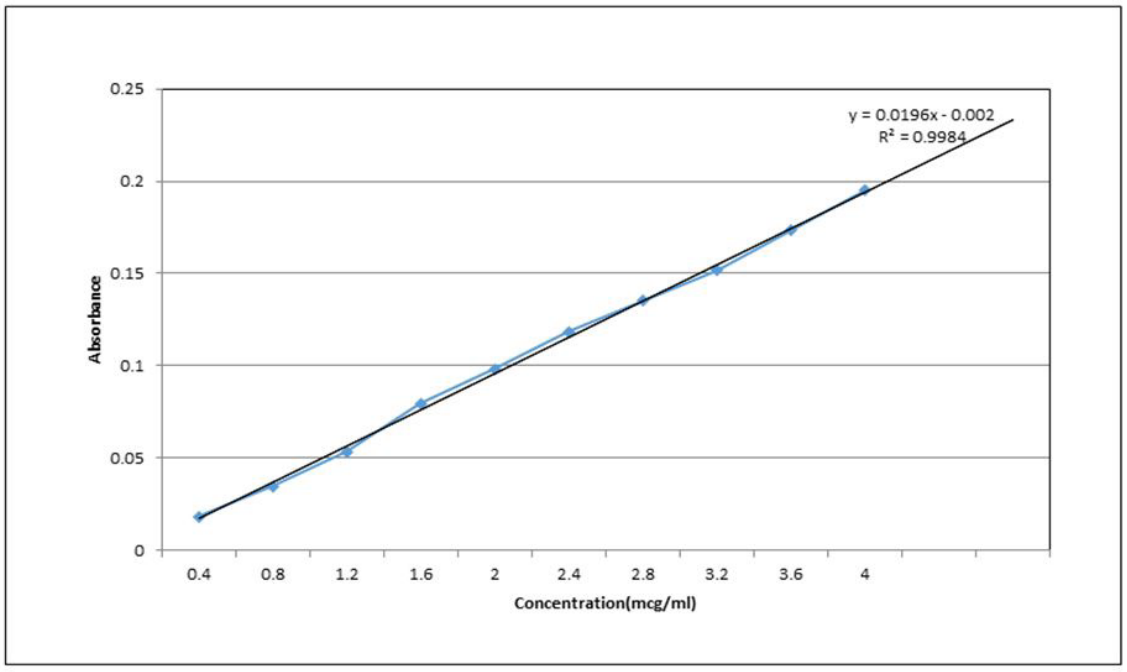

Figure 5: Standard Calibration Curve of Fluoxetine Hydrochloride

Formulations	Drug Content (%)	
	HPMC15CPS	HPMCK4M
F1	99.473±0.84	93.508±0.84
F2	98.070±0.71	97.456±0.54
F3	99.912±0.62	85.00±0.78
F4	91.842±0.61	86.228±0.83
F5	100.175±0.46	85.789±0.75
F6	97.982±0.97	98.947±0.37
F7	91.491±0.73	93.157±0.58
F8	94.736±0.52	99.385±0.45
F9	99.210±0.89	96.842±0.87

Data are expressed as mean ± standard deviation (n=3)

Table 6: Drug content of formulations prepared by using HPMC 15cps and HPMC K4M

In-vitro drug release study

The drug release profile of formulations prepared by both polymers i.e., HPMC 15CPS and HPMS K4M are shown in Figures 6,7,8,9,10,11,12 and 13 respectively. In the formulation prepared by HPMC 15CPS, the maximum release of the drug was occurred at around 3 minutes. Among all the formulations, F3 showed the highest percentage drug release which was 99.78% at 3 minutes.

Meanwhile, in another formulation prepared by HPMC K4M, the highest percentage of drug release was 99.23 % for F3 at around 6 minutes. Other formulations also showed maximum drug release at around 6-8 minutes.

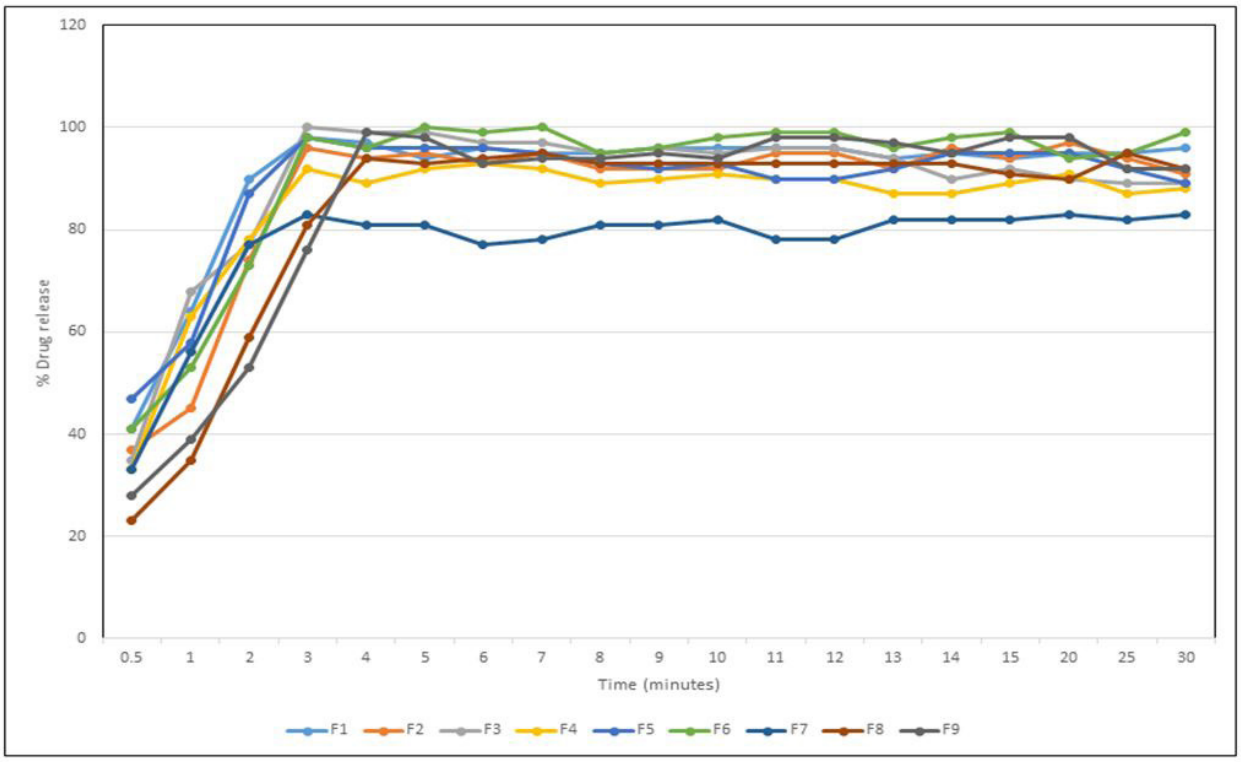

Figure 6: Zero-order release kinetics curve of percentage (%) release vs. time (min) of all formulations (F1-F9)

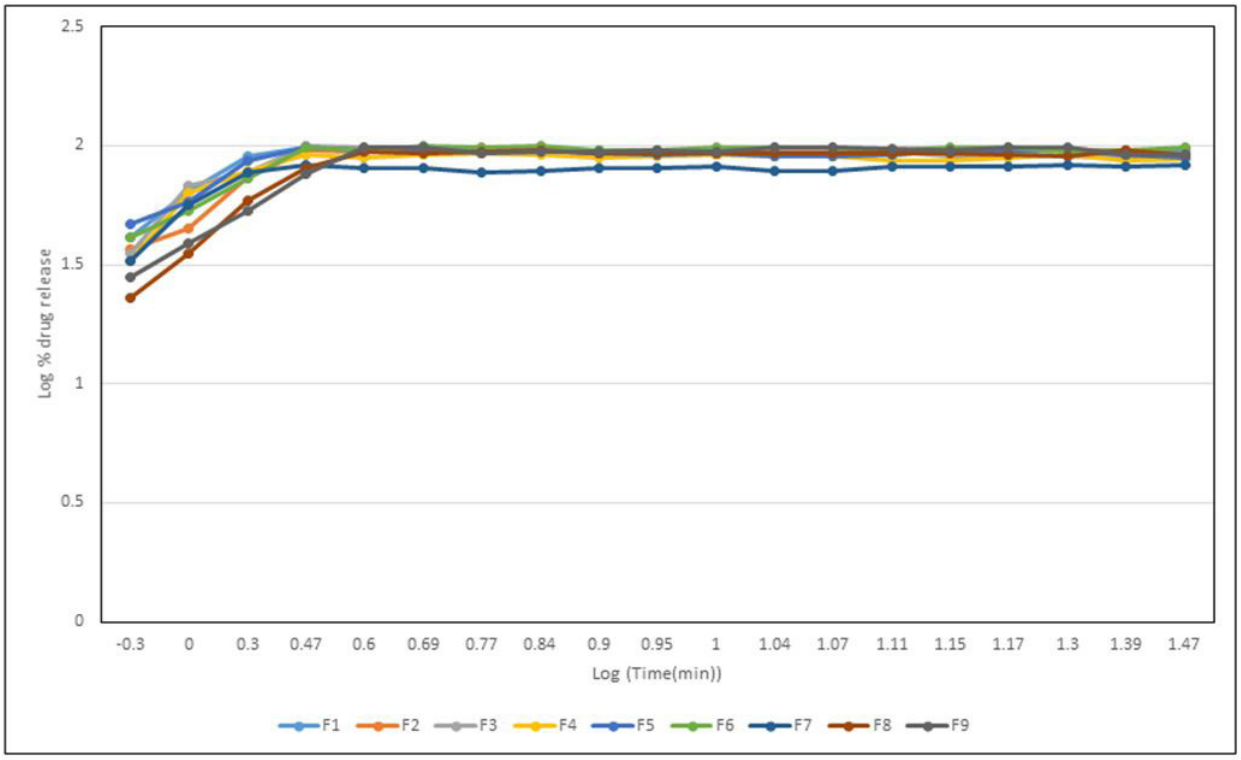

Figure 7: First-order release kinetics curve of log of % remaining vs. time (min) of all formulations (F1-F9) of HPMC 15CPS

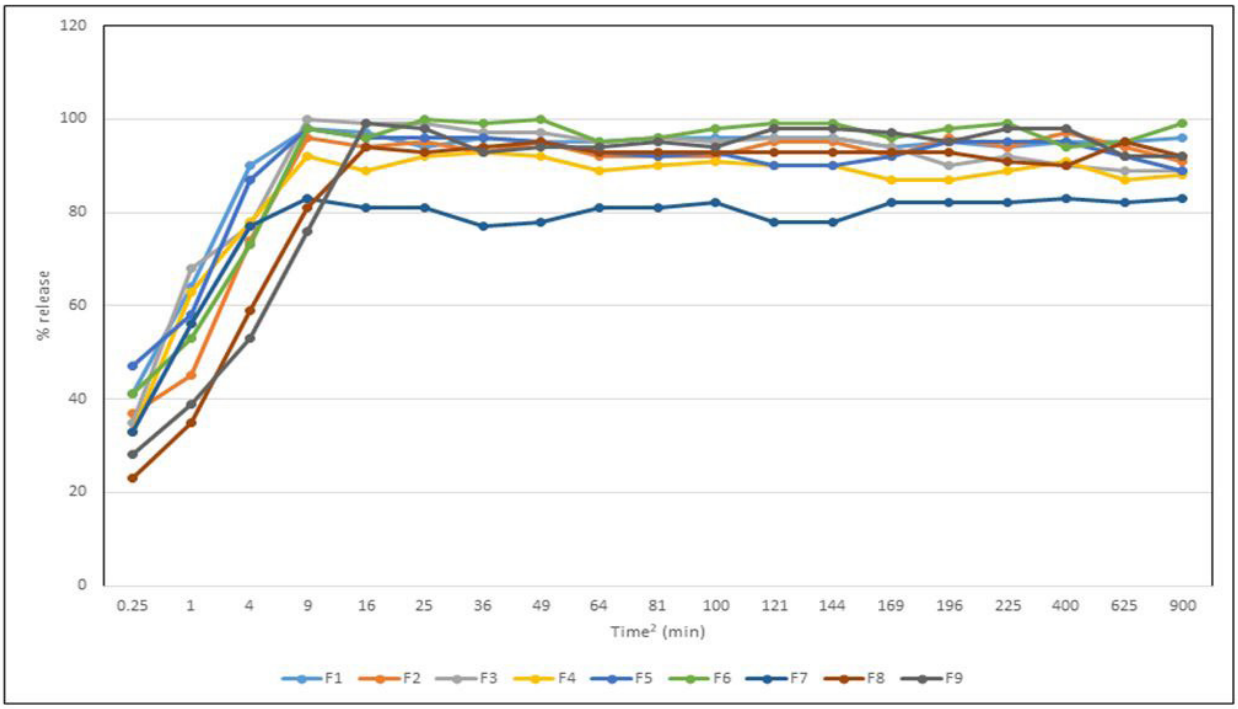

Figure 8: Higuchi release curve of % release vs. time^2(min) of formulations (F1-F9) HPMC 15CPS

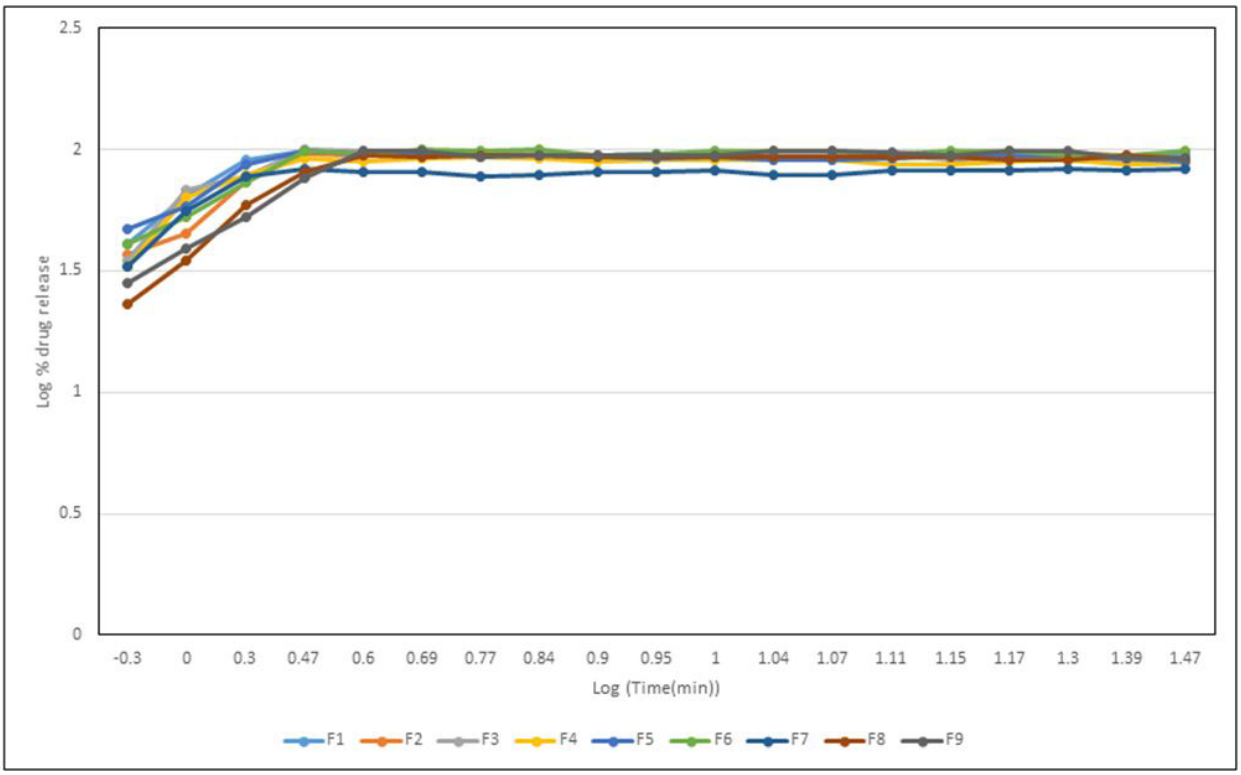

Figure 9: Korsmeyer's Peppa's curve of log of % release vs. log time (min) of all formulations (F1-F9) of HPMC 15CPS

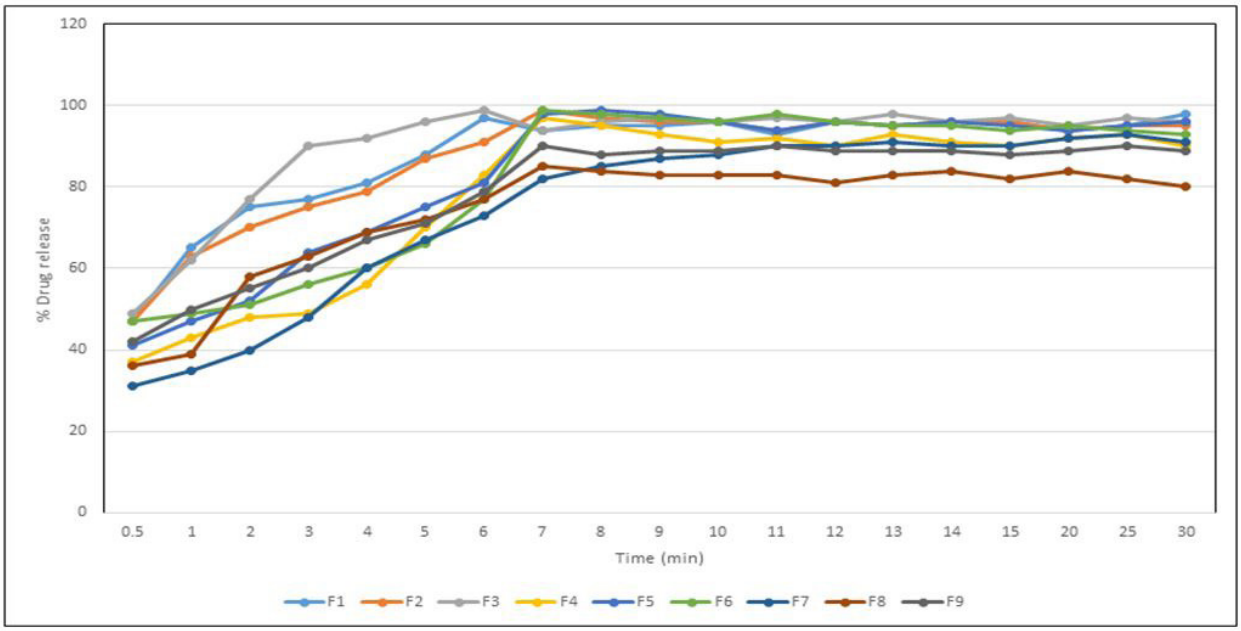

Figure 10: Zero-order release kinetics curve of percentage (%) release vs. time (min) of all formulations (F1-F9) of HPMC K4M

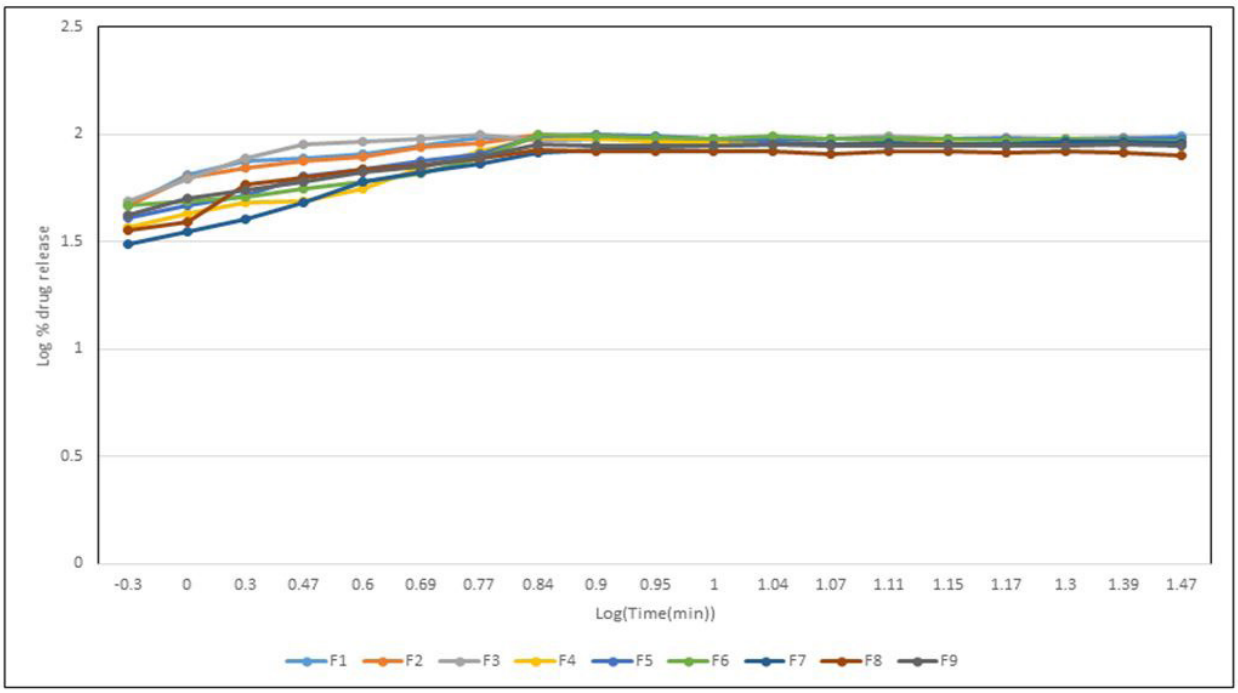

Figure 11: First-order release kinetics curve of log of % remaining vs. time (min) of formulations (F1-F9) of HPMC K4M

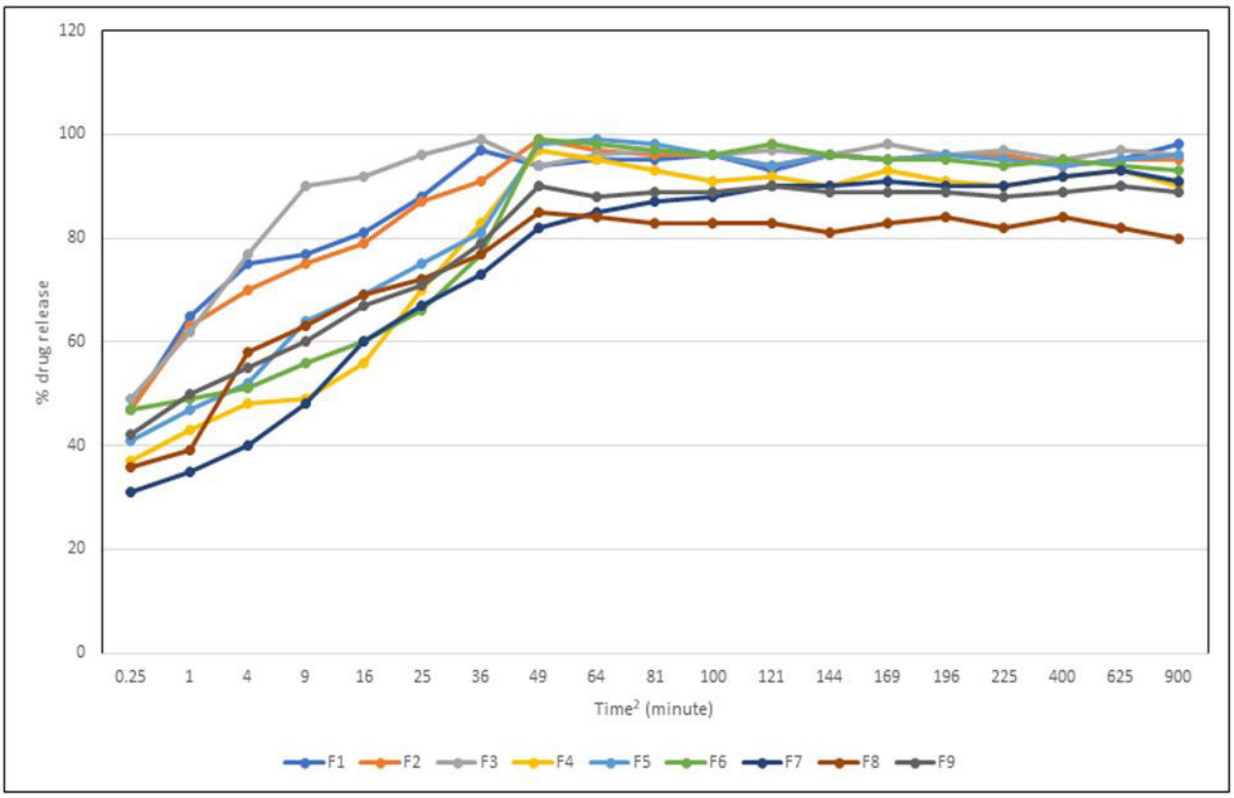

Figure 12: Higuchi release curve of % release vs. time^2(min) of formulations (F1-F9) of HPMC K4M

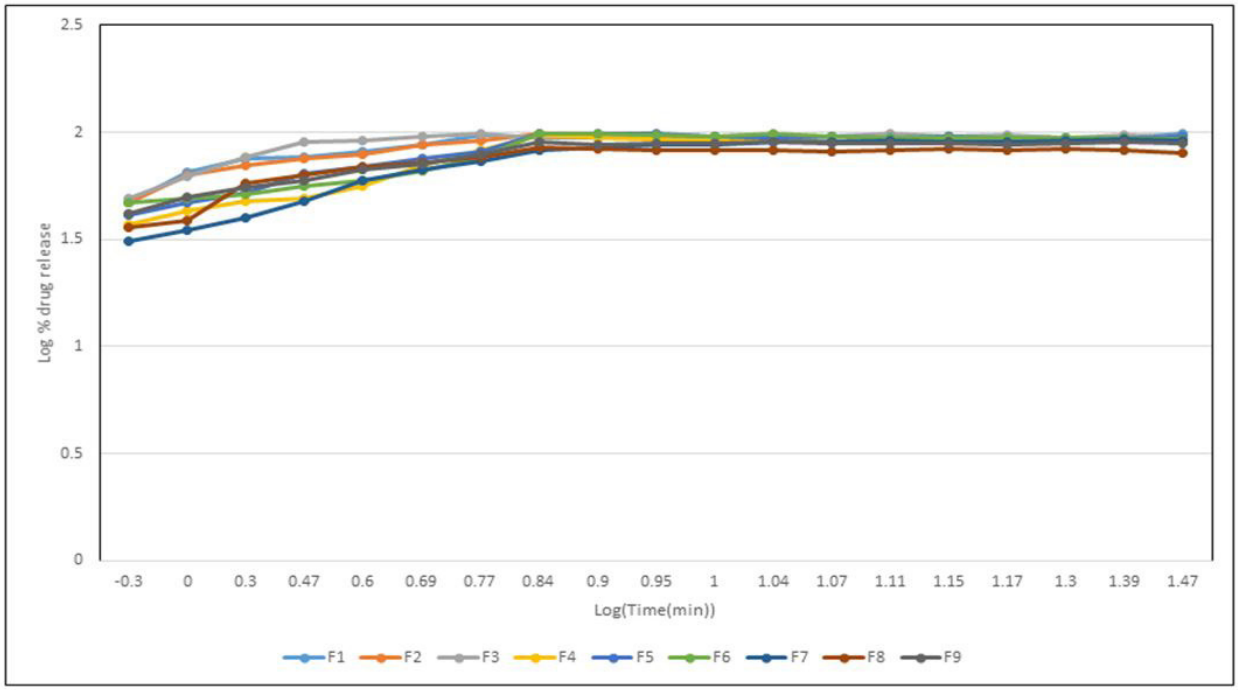

Figure 13: Korsmeyer's Peppa's curve of log of % release vs. log time (min) of formulations (F1-F9) of HPMC K4M

Discussion

Fluoxetine hydrochloride (FH) is a BCS class 1 drug with high solubility and high permeability. This drug is marketed widely in the tablet, capsule, and syrup form as a selective serotonin reuptake inhibitor (SSRI) for the treatment of pathological conditions related to the nervous system [26]. At the same time, the development of a modified or immediate-release formulation of FH for fast onset of action as well as to subside the shortcoming of the conventional dosage form is of utmost importance. Therefore, this study was conceived to add a brick to the study and design of FDOF of FH. The literature review was done to the determination of the compatibility of FH with HPMC 15CPS with HPMC K4M. In a study by Pakhale et al. 2019, formulation and evaluation of fluoxetine effervescent floating tablet was done with the use of HPMC K4M. The data from Fourier Transform Infrared Spectroscopy (FTIR) revealed that fluoxetine is compatible with all the excipients used [27]. In another study by Saleem et al. 2016, formulation and evaluation of microspheres of fluoxetine Hydrochloride using different biopolymers was done. The compatibility study from FTIR and Scanning Electron Microscopy (SEM) revealed that HPMC is compatible for designing formulation with FH [28]. Based on these experiments HPMC 15CPS and HPMC K4M were selected to further carry out the research.

In a study by Mahbood et al. 2016, the review highlighted that the FDOF prepared with the polymer HPMC 15CPS and HPMC K4M have physically appeared as transparent and film-forming capacity is average [29]. The experimentally formed films were also found to be transparent, smooth, odorless, clear, and flexible which met the standard mention criteria of the physical appearance of the oral film. Similarly, the USP guideline denotes that the formulation will meet the criteria of the weight variation test if it does not deviate more from the average weight [30]. In our study, the result demonstrated that the weight of films prepared by using HPMC 15CPS varies from 0.15g to 0.20g while the weight of film prepared by HPMC K4M varies from 0.14g to 0.16g which lies within the acceptable range. This result even demonstrated that the weight of the film gets varied with the change in the polymer which coincides with the result as mentioned by Devi et al, 2016 [31].

In a study performed by Gorsuch et al. 2010, the effect of different polymers on the thickness of FDOF was studied. The study revealed that after drying of FDOF of caffeine citrate and caffeine base there was no significant difference in the thickness of the film. However, the thickness got varied with the change in polymer concentration which resembled that the thickness of FDOF does not depend on the type of polymer used but gets altered with the change in polymer concentration [32]. The study also

showed that with the increase in the concentration of polymer, a slight upsurge in the thickness of the film was observed. On the other hand, Tomar et al. 2012, demonstrated that if the surface pH of FDOF becomes either acidic or basic, then the film can irritate the buccal mucosa. Therefore, the prepared film should lie in the range of neutral pH from 6.5 to 7.5 which is fairly comfortable for the administration [33]. The film prepared in our study with the use of both polymers also lies in this range which shows that the films prepared are pH acceptable.

Followingly, the study by Irfan et al. 2016, mentioned that direct relation exists between mechanical strength and folding endurance of films. As mechanical strength is governed by the plasticizer concentration, the change in plasticizer concentration also indirectly affects folding endurance [34]. The prepared film in this study showed a folding endurance of greater than 150. The value of folding endurance revealed that the prepared films are suitable for general handling. Meanwhile, in another study by Al-Mogherah et al. 2020, the moisture content in the FDOF of venlafaxine hydrochloride was done. The study demonstrated that the moisture content of the film lies in the range of 0.66% to 5.69%. The study even mentioned that the extent of moisture uptake depends upon the concentration of hygroscopic excipients present such as glycerol [35]. In this study, the moisture content value of oral film ranges from 1.33 -2.40% which is favorable to maintain the suppleness and thus prevent drying, brittleness, bulkiness, and microbial contamination.

A study by Kunte et al. 2010, the study mentioned that FDOF is a solid dosage form that disintegrates or dissolves within 1 minute when placed in the mouth without drinking water or chewing. This disintegration mechanism allows the drug to bypass the first-pass metabolism thereby making the medication more bioavailable [36]. In another study by Liew et al. 2013, the effect of polymer, plasticizer, and filler on orally disintegration film was studied. The study demonstrated that the disintegration time of film gets decreased correspondingly to decrease in tensile strength of the film and the increase in HPMC concentration result in the upsurge in tensile strength. Therefore, the study showed that an increase in HPMC concentration results in a rise in disintegration time [37]. This data gets to coincide with our study as well in which an increase in the concentration of HPMC increases in the disintegration time. But the study showed that disintegration time for the film prepared with polymer HPMC 15 CPS is much lower as compared to that of the polymer prepared with HPMC K4M. This may be due to the viscous nature of HPMC K4M, as viscosity and swelling time are directly proportional which subsequently increase the disintegration time. The result also demonstrated that a stepwise increase in the concentration of super disintegrants causes a decrement in the disintegration time which allied with the study by Yellanki et al. 2011 [38]. Similarly, for the study about content uniformity, any standard method described for the API in any of the standard pharmacopeias should be taken for the reference basis. Content uniformity is determined by estimating the API content in the individual strip. The limit of content uniformity is 85-115%. The drug content in all the films prepared using HPMC 15CPS and HPMC K4M were found to be between 90 -100% and 85 -99 % respectively. As per the USP requirements, the films were found to meet the criteria for content uniformity of 85-115 % of the labelled claim. Similarly, the result even demonstrated that there was no significant difference in the drug content among all the films which indicate that the drug was dispersed uniformly throughout the entire films.

A study by Rajasree et al. 2017, revealed the effect of different polymers on the drug release behavior of fast dissolving oral film of Amlodipine Besylate. The study used polymers such as hydroxyl propyl methylcellulose, polyvinyl alcohol, and sodium alginate. The result in the study revealed that the release rate of the drug is greatly altered with the change in type and concentration of polymer[39]. The result revealed that as the concentration of film-forming agent increases in the formulation, the release rate of the drug gets decreases. Among all the formulations of HPMC 15CPS, formulation F3 showed the highest amount of drug release at 3 minutes. This result coincides with the lowest amount of the polymer used and the highest amount of super disintegrant used. Meanwhile, likeliness in the result was also found in the formulations of HPMC K4M of which formulation F3 showed the highest amount of drug release at 7 minutes. In the comparison of the two formulations prepared, formulations of HPMC 15 CPS showed better drug release at a lesser time than that of HPMC K4M which may be due to the highly viscous nature of HPMC K4M.

Conclusion

Fast dissolving oral film (FDOF) is an emerging dosage form to minimize the pitfall of a conventional dosage form such as first-pass metabolism, suffocation or choking, etc. Meantime, the preparation of FDOF of the nervous system acting drugs like Fluoxetine hydrochloride (FH) is a quality approach for the efficient, rapid, and convenient treatment of infirmity such as unipolar and bipolar depression, bulimia nervosa, etc. This study utilized two different compatible polymers, HPMC 15CPS and HMC K4M which have different viscous properties. The result obtained highlight the feasibility of using these polymers for the preparation of oral films. The disintegration time of films formed by HPMC K4M is higher than that of HPMC 15CPS which is attributed to the high viscosity of HPMC K4M.

On the other hand, an in-vitro drug release study showed that formulation containing polymer HPMC 15CPS showed more immediate drug release at around 3 minutes as compared to other formulations which contain polymer HPMC K4M and release drug at around 6 to 8 minutes. This highlights the role of polymer in the drug release profile. With this formulation and in-vitro characterization, this study paved a footstep for the development of FDOF of FH. Further, the in-vitro and in-vivo pharmacokinetic and therapeutic study of the prepared film will ease to authenticate the efficacy and bioavailability of the fast-dissolving oral film of fluoxetine hydrochloride.

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Author Contribution

Pramila Acharya, Sudina Manandhar and Prativa Shahi conceived and designed the experiments. Pramila Acharya, Sudina Manandhar, Prativa Shahi, Bishnu Gurung, Anisha Lamichhane, and Rishiram Baral performed the experiments. Shila Gurung supervised the research activity and set up the methodology of the experiment. Pramila Acharya, Sudina Manandhar, Bishnu Gurung, and Rishiram Baral analyzed the data. Rishiram Baral wrote the paper.

Conflict of Interest

The author declares no conflict of interest.

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