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Original Article

Controlled-Release Low Density Effervescent Floating Matrix Tablets of Risperidone: Development, Optimization, *in vitro-in vivo* Evaluation in Healthy Human Volunteers and Determination of Dissolution Equivalency

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Abstract

The main objective of the present study was to formulate gastroretentive effervescent sustained release drug delivery systems of risperidone floating tablets with the help of Methocel® K15, Ethocel® standard 7FP premium, Eudragit ® RS100 sustained release polymers to improve its safety profile, bioavailability and patient compliance. Risperidone floating tablets were formulated by wet granulation technique by using citric acid and sodium bicarbonate as a gas generating agent. Methocel® K15, Ethocel® standard 7FP premium, Eudragit® RS 100 were used to formulate floating effervescent sustained release tablets. Preliminary trials were done to investigate matrix integrity and floating behavior. On the basis of preliminary trials, various formulations were designed to optimize the best formulation. The FDA recommended statistical approach was used to test dissolution equivalency. Preliminary studies showed better floating behavior, but poor matrix integrity with Methocel®K15 containing formulations. Moreover, Ethocel® standard 7FP premium and Eudragit® RS 100 containing formulations showed better matrix integrity but poor floating behavior. Formulations RSFTIII, RSFTVI, RSFTIX were optimized and showed the drug release for 10 hours. Dissolution equivalency was tested for optimized formulation and found equivalent. *In vivo*-study also showed gastric retention time more than 4 hours.

Keywords: Antipsychotic drug, Dissolutionequivalency, Eudragit RS 100, Ethylcellulose, Floating drug delivery system, Gastroretentive drug delivery system, Hydrodynamically balanced system, Risperidone.

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1. Introduction

Gastroretentive dosage form is a kind of novel drug delivery system, dosage formremains in the stomach for an extended period of time by prolonging the gastricresidence time of the drug [1].Gastroretention is very vital for those drugs that have a very likely absorption window into the stomach, drugs that are not well absorbed or degraded at intestinal higher pH.It is also beneficial for those drugs having absorption altered by change in gastric emptying time [2].

Table 1. Formulation of risperidone floating tablets for preliminary trials.

Formulation	Drug	HPMC K15	Ethocel	Eudragit RS100	NaHCO3	Citric Acid	Lactose (M.H)	Magnesium stearate	IPA	Remark
I	6	**22.5**	-	–	25	10	83.5	3	0.1ml	Float
II	6	**30**	-	–	25	10	76	3	0.1ml	Float
III	6	**37.5**	-	–	25	10	68.5	3	0.1ml	Float
IV	6	–	**22.5**	–	25	10	83.5	3	0.1ml	–
V	6	–	**30**	–	25	10	76	3	0.1ml	–
VI	6	–	**37.5**	–	25	10	68.5	3	0.1ml	Float
VII	6	–	–	**22.5**	25	10	83.5	3	0.1ml	–
VIII	6	–	–	**30**	25	10	76	3	0.1ml	–
IX	6	–	–	**37.5**	25	10	68.5	3	0.1ml	–

While extended release drug delivery systems show some limitations like short retention time, poor gastric emptying time. These limitations result in too rapid and variable gastrointestinal transitwhich may lead to incomplete drug release from the device into the absorption window. As a result of whichadministered dose show diminished efficacy [3, 4].Floating drug delivery system (FDDS) is a type of gastroretentive drug delivery system and also known as a hydrodynamically balanced system (HBS). FDDS produces carbon dioxide gas on coming in contact with the acidic gastric fluid, as a result, theentrapment of gas in a swollen matrix causes reduction in the density of the system which causes the system tofloat over gastric fluid and to release the drug slowly for a prolonged period of time at a desired rate [5]. This system has a bulk density less than that of the fluid inside the stomach, thus buoyant for want of disturbing the Gastric emptying rate (GER) for an extended period of time while the drug is released gradually and slowly. It is specifically targeted delivery system to achieve local and systemic effects by release of drug in the upper gastrointestinal tract, also improves drug availability to its absorption site, decrease wastage of drug and improves solubility of poor soluble drugs that are poorly soluble in the stomach [6, 7, 8, 9, 10, 11, and 12]. Risperidone, a second-generation antipsychotic drug, is widely used in the clinical management of schizophrenia, bipolar and irritability disorders. Risperidone lipophilic in natureis rapidly and completely absorbed orally and extensively metabolized by cytochrome P450 2D6 into a major metabolite 9-Hydroxy-risperidone. 9-Hydroxy-risperidone is pharmacological as much potential as that of the parent compound. The serum concentration of the active moiety is thus the sum of serum concentrations of risperidone and 9-hydroxy-risperidone [13,14].Risperidone has an elimination half-life of 3 hours in extensive metabolizers and 17 hours in poor and extensive metabolizers [15]. A dose of 4-8 mg per day is recommended for getting maximum efficacy with minimum adverse drug reactions [16]. Patient compliance is likely poor in the case of therapy with antipsychotic drugs [17].

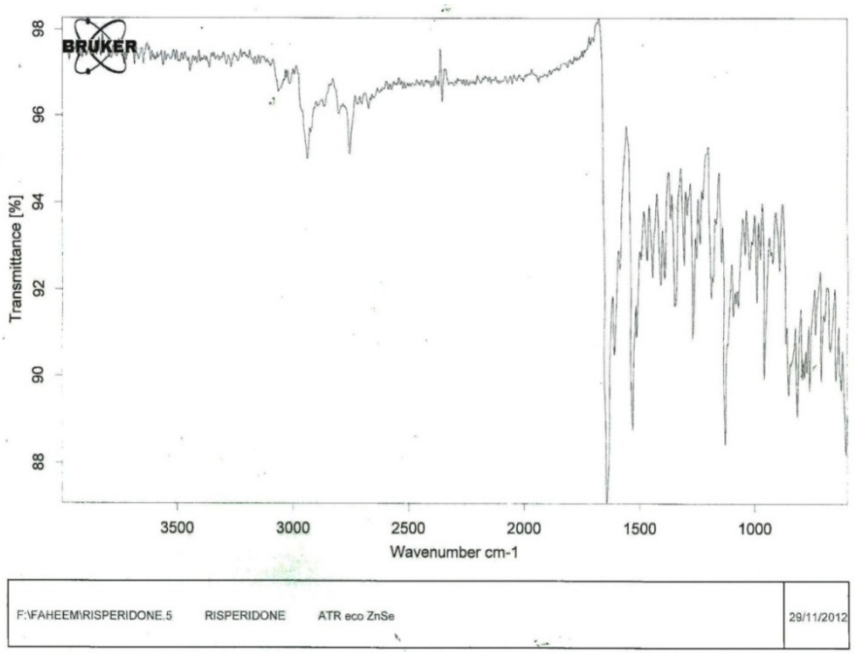

Figure 1. FTIR spectra of risperidone.

Non adherence to antipsychotic drug therapy is mainly due to their extrapyramidal side effect [18]. As described earlier, risperidone is lipophilic in nature and having better solubility

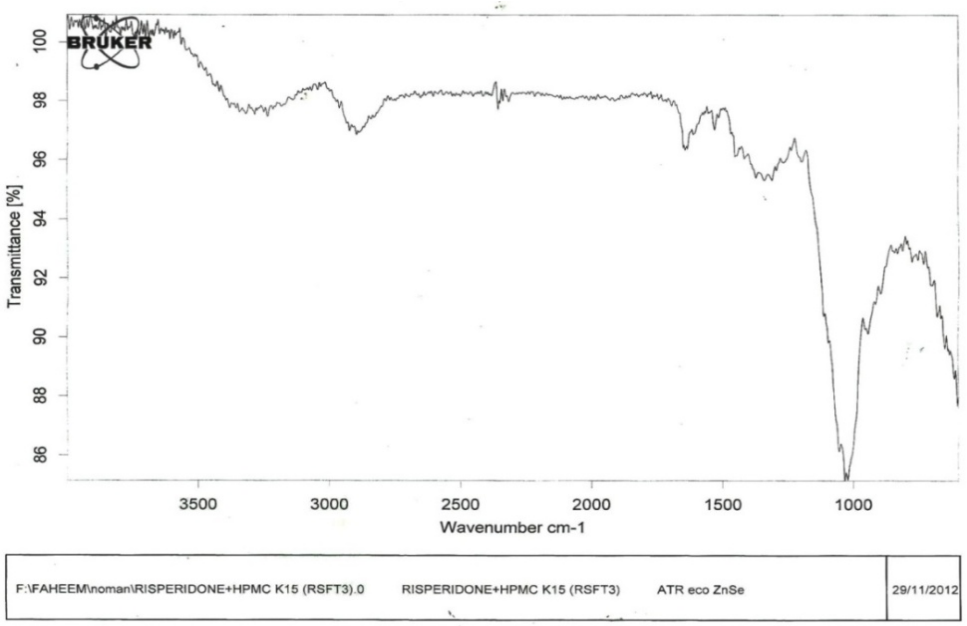

Figure 2. FTIR spectra of risperidone + HPMC K15.

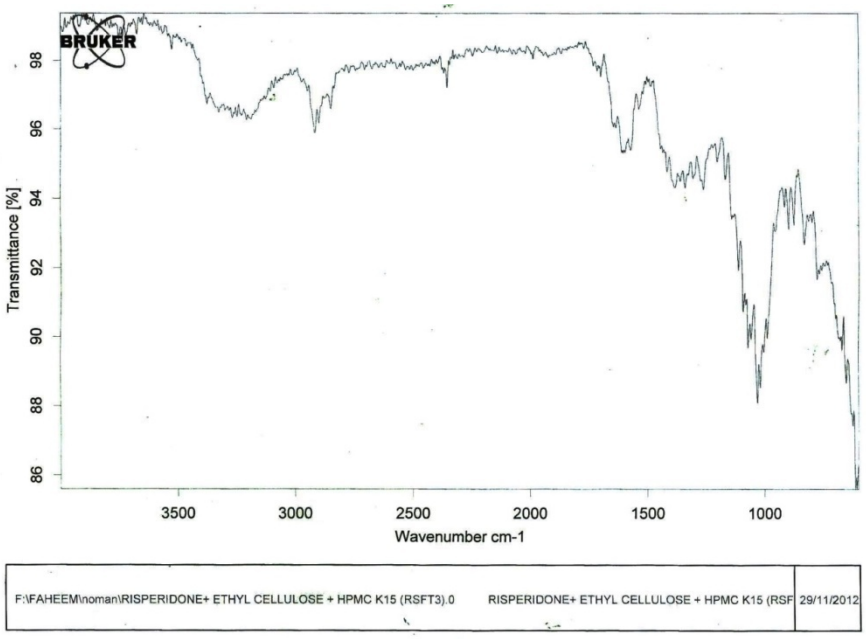

Figure 3. FTIR spectra of risperidone + HPMC K15 +Ethylcellulose.

in the acidic environment of the stomach. For avoiding non adherence; improving optimum drug availability and also for minimizing side effects, floating matrix tablet of risperidone was decided to beformulated.AmirBadshah*et al*. formulated controlled release matrix tablet of respiration by using Methocel® K100 LV-CR and Ethocel® standard 7FP premium to optimize its blood level, minimize its side effects, and ultimately improve its treatment adherence [19].Risperdal consta was formulated by Janssen-Cilaghaving extended

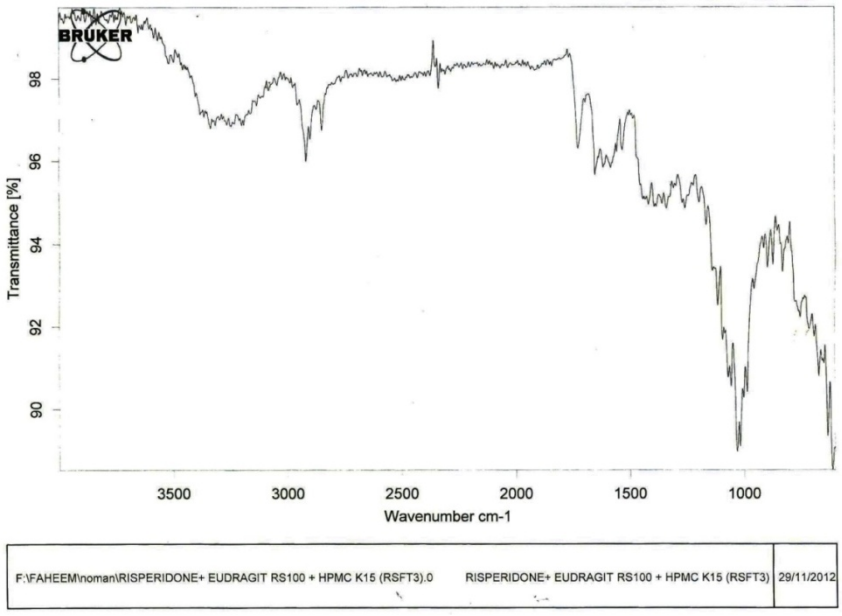

Figure 4. FTIR spectra of risperidone+ HPMC K15+Eudraguit RS100.

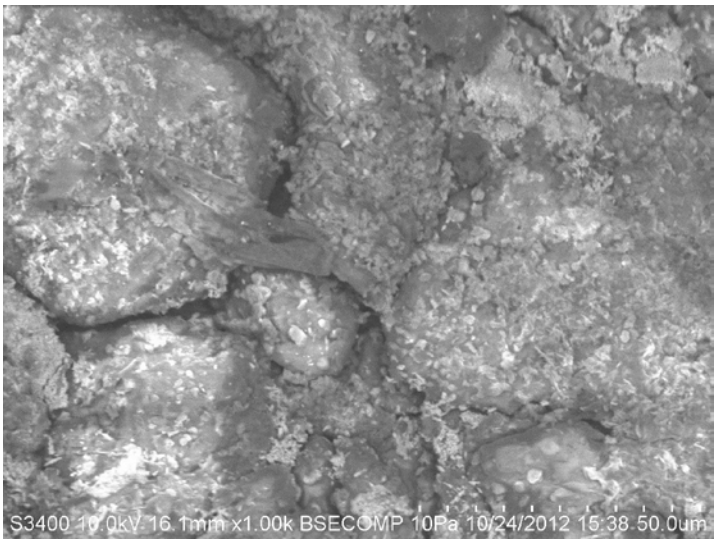

Figure 5. SEM of dry tablet (RSFTVI).

release microspheres formulation of risperidone micro-encapsulated in polyglactin for intramuscular injection for long term treatment of schizophrenia.

Tabandeh*et al*. formulated sustained release matrix tablet of aspirin with Ethylcellulose, Eudragit RS100 and Eudragit S100.Ethylcellulose was found to beindependent of moderate changes in hardness [21].

2. Materials and Methods

2.1 Materials

Risperidone, Methocel® K15 (HPMCK15), was provided by Mediceenapharma, Lahore,

Table 2. Formulation of floating tablets of risperidone.

Formulation	Drug	HPMC K15	Ethocel	Eudragit RS100	NaHCO3	Citric Acid	Lactose (M.H)	Magnesium stearate	IPA	Remarks
RSFTI	6	75	-	-	25	10	31	3	0.1ml	Float
RSFTII	6	82.5	-	-	25	10	23.5	3	0.1ml	Float
RSFTIII	6	90	-	-	25	10	16	3	0.1ml	Float
RSFTIV	6	45	22.5	-	25	10	38.5	3	0.1ml	float
RSFTV	6	52.5	22.5	-	25	10	31	3	0.1ml	Float
RSFTVI	6	60	22.5	-	25	10	23.5	3	0.1ml	Float
RSFTVII	6	45	-	22.5	25	10	38.5	3	0.1ml	Float
RSFTVIII	6	52.5	-	22.5	25	10	31	3	0.1ml	Float
RSFTIX	6	60	-	22.5	25	10	23.5	3	0.1ml	Float

Pakistan as a gift.Ethocel® standard 7FPPremium (Ethylcellulose) (Dow Chemical Company) was obtained as a gift from the Allied Pakistan. Lactose monohydrates (Meggle, Germany), citric acid anhydrous (Aldrich Chem. Co. Ltd., England) have been used.

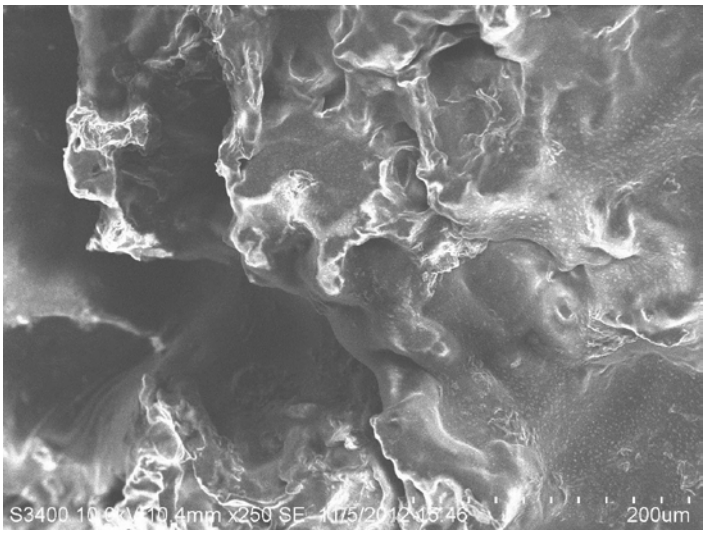

Figure 6. SEM of wet tablet (RSFTVI.

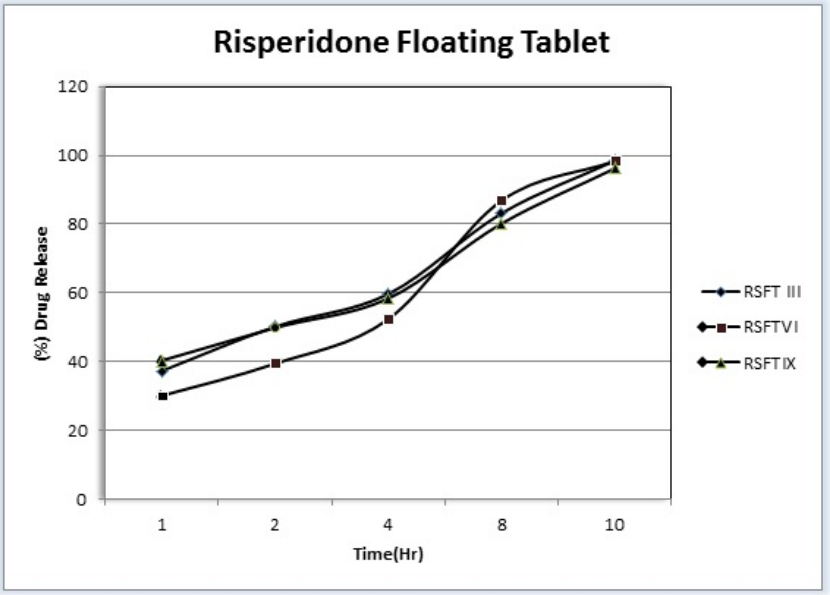

Figure 7. Release kinetics profile for optimized formulations RSFTIII, RSFTVI & RSFTIX.

Chemical; Pakistan.Eudragit® RS 100 (Evonic industries) was also received as a gift from Lahore chemical pharmaceutical works, Lahore,

Tablets were prepared by wet-granulation technique. Risperidone was mixed withdesired quantity of Methocel K15 or Eudragit RS 100 or

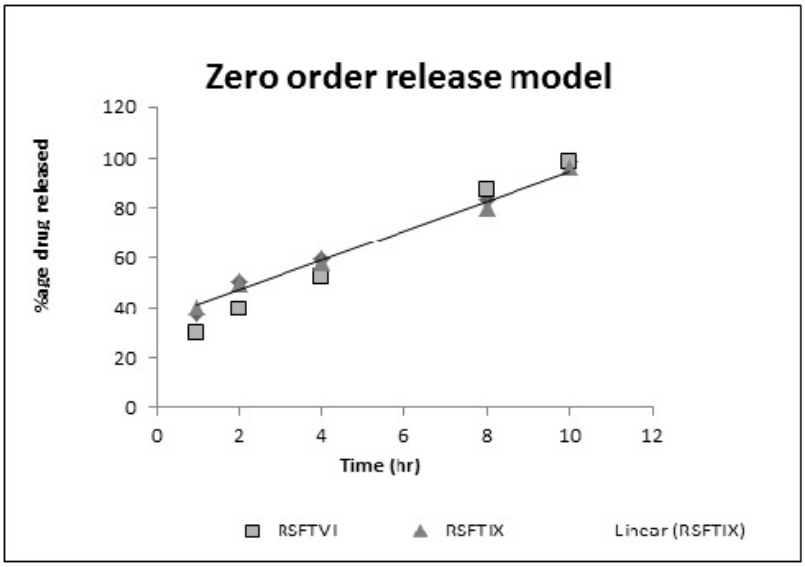

Figure 8. Zero order release kinetics model of risperidone formulation RSFTIII, RSFTVI& RSFTIX.

Table 3. Postcompression parameters for formulations FRT1-FRT9.

Preparations	Hardness (Kp)	Diameter (mm)	Thickness (mm)	Uniformity in Weight (%)	Drug Content (%)	Friability (%)
FRT1	4.4±2.46	9.12±0.01	3.41±0.04	1.2±0.29	98.7±0.76	0.42±0.42
FRT2	5.04±0.83	9.15±0.03	3.78±0.01	1.44±1.27	96.73±0.61	0.58±0.5
FRT3	5.65±0.02	9.25±0.01	3.82±0.02	2.65±2.93	99.32±0.52	0.37±0.45
FRT4	5.6±0.93	9.21±0.02	3.72±0.01	1.33±0.96	96.44±0.70	0.27±0.53
FRT5	4.8±0.06	9.12±0.01	3.68±0.3	1.76±2.01	98.55±0.59	0.22±0.5
FRT6	5.2±0.43	9.16±0.13	3.73±0.02	1.43±0.37	95.87±0.48	0.17±0.47
FRT7	5.2±1.05	9.14±0.1	3.63±0.01	1.76±0.52	97.99±0.85	0.23±0.61
FRT8	6.2±0.23	9.2±0.03	3.84±0.02	1.48±1.05	99.76±0.99	0.32±0.43
FRT9	5.4±0.64	9.17±0.01	3.74±0.01	1.98±1.88	97.84±0.54	0.12±0.4

Ethocel standard 7FP premium and lactose

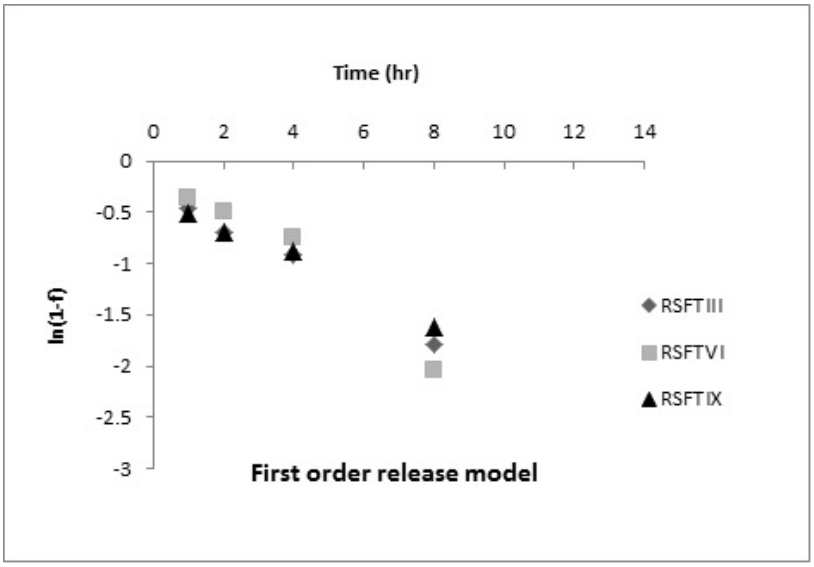

Figure 9. First order release kinetics model of risperidone formulation RSFTIII, RSFTVI &RSFTIX.

M.H.Above mentioned all excipients were thoroughlymixed and granulated with0.5ml IPA. The wet mass was passed through sieve having mesh-16 and dried at (45C°-50 C°) for (30-45 min). Then the grains were passed through sieve having mesh-30 and mixed with magnesium stearate as lubricant. Finally, the granules were compressed into tablets by using (9mm) punch tablet compressionmachine. In preliminary studies, the preliminarytrials were conductedto find out the effects of differentpolymer on the drug release having polymer concentration of

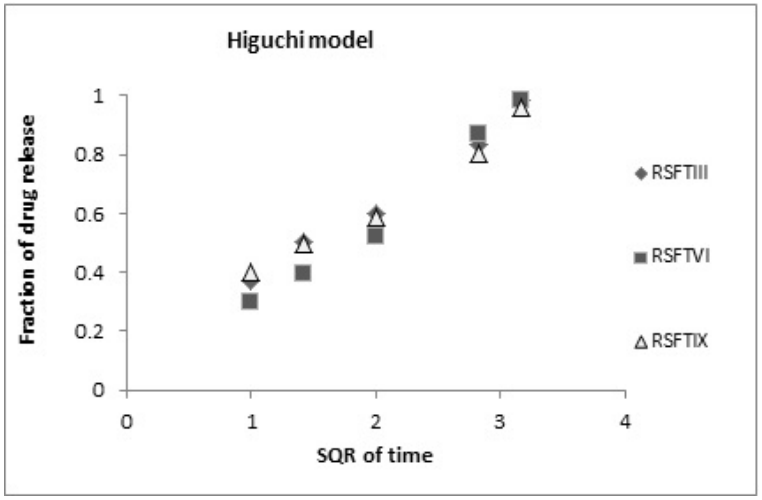

Figure 10. Higuchi release kinetics model of risperidone formulation RSFTIII, RSFTVI &RSFTIX.

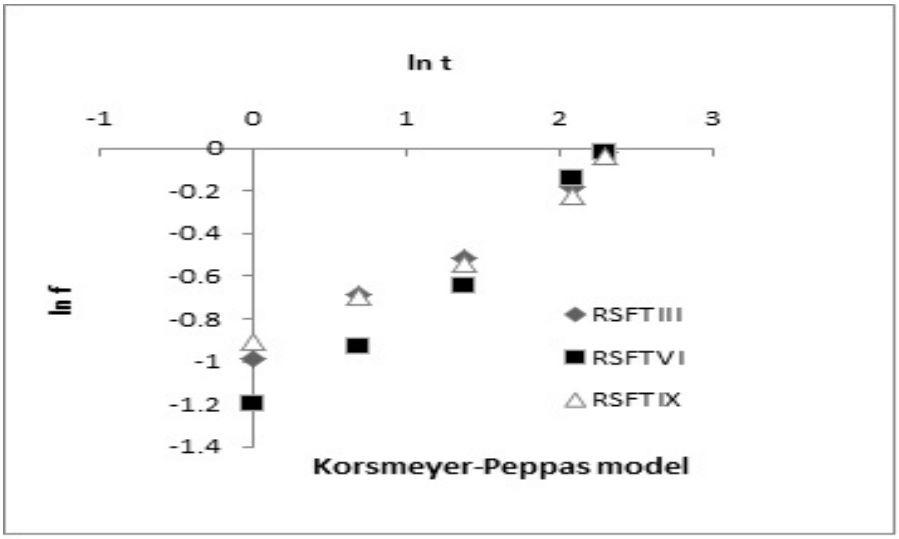

Figure 11. Korsmeyer-peppes release kinetics model of risperidone formulation RSFTIII, RSFTVI & RSFTIX.

15%, 20%, 25% &weight of the tablet was 150mg (Table 1).While, all the formulations were contained 6mg risperidone, 17% sodium bicarbonate and citric acid anhydrous as gas producing agent, lactose monohydrate as diluent and magnesium stearate as a lubricant. Dissolution of all the formulations in Table 1(preliminary formulations) was carried out. It was assumed that the concentration and polymeric type imparted sustained release action of the drug. Various polymers were investigated and found to be unsuitable for formulating floating tablets because of their lack of abilities to form matrix or poor floating shown by the formulations containing those particular polymers (Table 1). Higher concentration of Methocel K15 (50%, 55%, 60%) and a combination of Methocel K15 (30%, 35%, 40%) with ethicalstandard 7FP premium (15%) and EudragitRS100 (15%) were formulated respectively (Table 2).

2.3. Evaluation of Powder Blend

Precompression study for the powder blend includes, loose bulk density, tapped density, angle of repose, and compressibility index, and Hausner's ratio was calculated.

2.4. Evaluation of Floating Matrix Tablets

Tablets were evaluated for post compression parameters like hardness, friability, uniformity of drug contents and uniformityofmassof single dose preparationas per US Pharmacopeia (USP).

2.4.1. In Vitro Buoyancy Studies

2.4.1.1. Buoyancy Lag Time

In vitro buoyancy studies include buoyancy lag time, total floating duration, and matrix integrity study and swelling index. The in vitrobuoyancy was examined by the method used by Rosa et al. [22] .The tablets were examined by taking in a 250 ml beaker having 0.1N HCl (pH 1.2). The time taken by the tablet to come up to the surface was noted and termed

as floating lag time and total floating duration was also observed visually by dissolution study.

2.4.1.2 Matrix Integrity

Matrix integrity was determined by visualizing *in vitro* dissolution study.

2.4.1.3 Swelling Index

Swelling properties of matrix tablets were studied by estimating water uptake by the polymer. Tablets are immersed in 0.1 N HCl at 37°C. Swelling index is measured in terms of percent weight gain as given by equation below,

Swelling index (S.I) = {(Wt-Wo) / Wo} x 100 (1)

Where, Wt. =final weight of the tablet at time t and Wo=initial weight of the tablet.

Tablets were removed at intervals of 2, 4, 6, 8 and 10hrsFirstly, excessive water was blotted with help of tissue paper and tablets were weighed. Water uptake is measured in terms of percent weight gain [23]. This data is provided in Table 7.

2.4.2. In Vitro Drug Release Studies

In vitro drug release studies were done by a dissolution test using of 0.1N HCl of pH 1.2 as dissolution medium. The temperature of the dissolution medium was maintained at (37°C±0.5°C), paddle speed was at the rate of 50 rpm. With each sampling, 5ml of the sample was taken and replaced by 5 ml fresh dissolution media by using a graduated pipette. Sampling was carried out after 1, 2, 4, 8, 10 hrs. intervals. The taken samples were analyzed for estimating assay for release risperidone at wavelength 271 nm using UV-Visible spectrophotometer (Shimadzu, Japan) [24, 25].

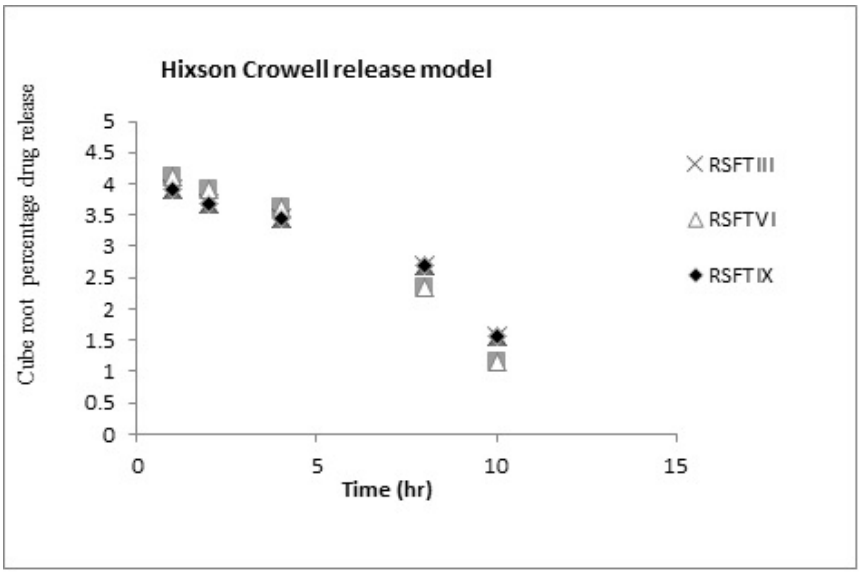

Figure 12. Hixson Crowell release model of risperidone formulation RSFTIII, RSFTVI &RSFTIX.

2.4.3. Kinetic Modeling of Drug Release

In order to examine the release mechanism of the drug from the optimized formulation (RSFTIII), (RSFTVI), and (RSFTIX) the results were fitted to release kinetic models. The regression coefficient R^2 value nearer to one indicated the model fitting of the release mechanism. Drug diffusion time and polymer chain relaxation are two key parameters determining drug delivery from polymer matrices. Zero order, first order, Higuchi, Hixson Crowell and KorsmeyerPeppas models are used to analyze the drug release pattern .The equations used in these models are as follows; Zero order release kinetics: cumulative % drug release = $K_0 t$ (2)

Where t is the time and K_0 is the Zero-order release constant. Zero order release kinetics is described as the process of by which constant drug release from a drug delivery system [26, 35].

First order kinetics: Log % unreleased drug = $K_1 t/2.303$ (3)

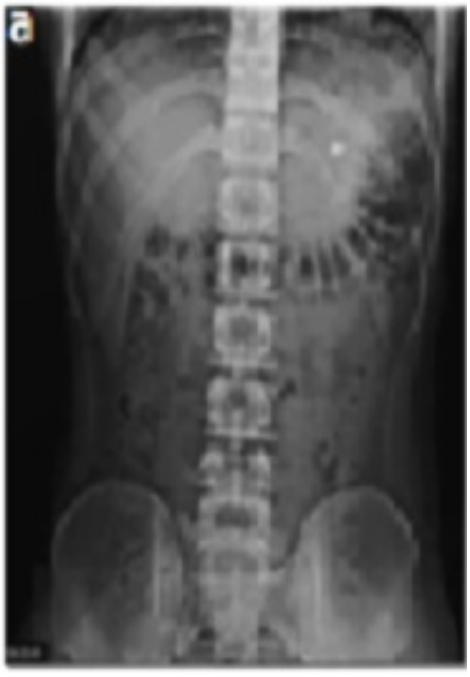

Figure 13. X-ray indicates the position of floating tablet in the gastrointestinal tract of volunteers a) X-ray taken at 1hr.

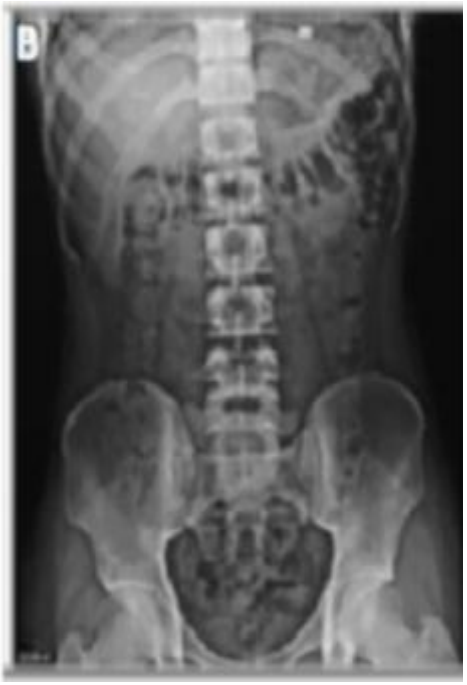

Figure 14. X-ray indicates the position of floating tablet in the gastrointestinal tract of volunteers. b) X-ray taken at 4 hr.

Table 4. Postcompression parameters for formulations RSFTI-RSFTIX.

Formulation	Hardness (Kp)	Diameter (mm)	Thickness (mm)	Weight variation (%)	Drug Content (%)	Friability (%)
RSFTI	5.43±0.45	9.12±0.02	3.72±0.02	2±1.31	97.87±0.91	0.21±0.73
RSFTII	6.00±0.38	9.17±0.04	3.71±0.03	1.34±0.91	97.33±0.63	0.38±0.62
RSFTIII	6.75±0.92	9.22±0.01	3.83±0.01	1.56±2.2	98.32±0.42	0.18±0.53
RSFTIV	4.32±0.06	9.11±0.03	3.4±0.01	2.2±2.8	98.32±0.04	0.11±0.48
RSFTV	4.78±1.01	9.12±0.15	3.67±0.02	1.8±1.06	97.43±0.21	0.12±0.57
RSFTVI	4.4±0.57	9.11±0.02	3.62±0.01	1.42±0.87	98.39±0.51	0.23±0.44
RSFTVII	4.7±0.86	9.15±0.01	3.65±0.01	1.7±0.91	99.45±0.12	0.13±0.65
RSFTVIII	4.62±0.69	9.13±0.02	3.62±0.02	1.54±1.70	96.65±0.37	0.16±0.51
RSFTIX	4.88±1.75	9.18±0.04	3.74±0.02	1.33±2.52	98.43±0.66	0.13±0.62

Where t time and k_1 is the first order release rate constant.

On hydrophilic matrix polymer undergoes simultaneously swelling and erosion mechanism and shows time dependent controlled release profile [27, 35].

Higuchi model: % drug released = $K_2 t^{1/2}$ (4)

t represents the time and K_2 is Higuchi constant. This model explains that: the initial concentration of the drug in the matrix is much higher than the solubility of the drug, the mechanism of drug diffusion occurs only in one direction, the particles of the drug are much smaller than system thickness and swelling of the matrix and dissolution are negligible [28,35].

Hixon Crowell Model: $Wo^{1/3} - Wt^{1/3} = KHCt$ (5)

Where KHC represents the Hixson - Crowell rate constant, Wt: percent drug release at time t, W0: percent drug present in the Tablets initially. This modelsuggests a change in its surface area as well as the diameter of the particles [29, 35].

KorsmeyerPeppas model: $MT/M\infty = K_p t^n$ (6)

Where K_p is release constant and n is the release exponent. The release exponent shows

Table 5. *In vitro* dissolution data for formulations FRT1-FRT9.

Formulations	Buoyancy Lag Time (sec)	Total Buoyancy time (hrs.)	Integrity of matrix	T_{50} Time for 50% of drug release ±SD (h)	T_{85} Time for 85% of drug release ±SD (h)
FRT1	**8**	**1**	**-**	**0.47±0.04**	**0.83±0.31**
FRT2	**7**	**1**	**-**	**0.42±0.20**	**0.82±0.02**
FRT3	**10**	**1**	**-**	**0.45±0.04**	**0.84±0.41**
FRT4	**-**	**1**	**-**	**0.51±0.02**	**0.88±0.11**
FRT5	**-**	**4**	**+**	**2.1±0.31**	**3.7±0.07**
FRT6	**-**	**8**	**+**	**3.97±0.04**	**7.52±0.43**
FRT7	**-**	**1**	**-**	**0.44±0.40**	**0.75±0.62**
FRT8	**-**	**1**	**-**	**0.43±0.01**	**0.78±0.11**
FRT9	**-**	**8**	**+**	**4.04±0.12**	**7.84±0.05**

Table 6**.** *In vitro* dissolution data for formulations RSFTI-RSFTIX.

Formulations	Buoyancy Lag Time (sec)	Total Buoyancy time (hrs.)	Integrity of matrix	T50±SD (h)	T85±SD (h)
RSFTI	7	1	-	0.46±0.09	0.78±0.03
RSFTII	9	4	-	2.27±0.45	3.84±0.32
RSFTIII	9	10	-	2.1±0.33	8.23±0.05
RSFTIV	11	1	-	0.39±0.18	0.89±0.37
RSFTV	13	1	+	0.33±0.61	0.89±0.81
RSFTVI	6	10	+	3.89±0.06	8.15±0.02
RSFTVII	15	1	-	0.40±0.51	0.83±0.22
RSFTVIII	32	4	-	0.45±0.02	0.81±0.02
RSFTIX	15	10	+	2.12±0.90	8.8±0.05

relaxation-controlled transport process as well as diffusion-controlled process [30, 35].

profiles. It can be mathematically computed by using the following formula:

Table 7. Degree of swelling of optimized risperidone floating tablet formulations.

Formulations	2^{nd}hr	4^{th}hr	6^{th}hr	8^{th}hr	10^{th}hr
RSFTIII	90.62±3.07	204±1.82	263.1±0.67	333.94±0.82	342.35±0.65
RSFTVI	83.54±1.03	213.33±1.66	264.516±1.7	361.33±0.73	387.5±0.78
RSFTIX	118.78±0.98	234.67±2.5	258.82±0.75	352.9±0.92	432.5±0.43

2.4.4 Testing Dissolution Equivalency

US-FDA recommended dissolution equivalency is computed by the estimation of similarity factor analysis as well as by difference factor analysis. The difference factor (f1) calculates the percent difference between the two dissolution profiles at each time point and measures the relative error between dissolution

$$f1 = \{[\Sigma_{t=1}^{n} |R_t - T_t|] / [\Sigma_{t=1}^{n} R_t]\} \times 100 \quad (7)$$

The similarity factor (f_2) was estimated between two formulations by using the data obtained from the drug release studies .The data were analyzed by the following formula.

$$f2= 50\times\log \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t-T_t)^2]^{-0.5} \times 100\} \quad (8)$$

Where n=number of time points, R_t and T_t= dissolution of reference and test products at time t.

The testing profiles are assumed similar having f_1-value near to zero while f_2-value more than 50 shows similarity into two dissolution profiles. Generally, if the value of difference factor is equal or less than 15 and the value of a similarity factor which is equal to or more than 50 indicates similarity between two dissolution profiles [31, 32, 33, 34].

2.4.5 In Vivo Evaluation of Gastrointestinal Residence Time of Risperidone Floating Tablets

X-Ray technique is also used as an evaluation parameter in the floating dosage form. It is used to locate the passage of dosage form in the gastrointestinal tract (GIT) that helps to predict and correlate the gastric emptying time and the passage of dosage form in the GIT. It is done with the inclusion of a radio-opaque material into a solid dosage form that enables it to be visualized by X-rays [31]. RSFTVI formulation has been selected for the *in vivo* study. Healthy volunteers were selected and were asked to take tablet with the help of sufficient water after meal. The x-ray was taken at different time intervals after one and four hours.

2.4.5.1 Tablet Preparation for In Vivo Studies

For the *in vivo* evaluation, for X-ray study, diameter of tablet was 9mm and 37 mg of the drug and lactose of the formulation was replaced with barium sulphate which is used as a radio contrast medium while other ingredients were kept constant. Actually, barium sulphate has high density and its addition into floating tablet formulation confers poor buoyancy.

2.4.6. FTIR Spectroscopic Analysis

Tablet samples were powdered that was mixed with KBr (Analytical grade) in the ratio 1:100 and further dried at 40°C. The mixture was compressed to a 12 mm semitransparent disk by applying a pressure of 65 kN (Pressure gauge, Bruker) for 2 min.That mixture was analyzed at wavelength range 4,500-400cm^{-1}. The FTIR spectrum was recorded by using an FTIR spectrometer (FT-IR Alpha-E, Bruker).

2.4.7 Scanning Electron Microscopic Studies (SEM)

The surface texture of the tablet was determined using scanning electron microscope S3400-N (Hitachi). The tablets were scanned by using a secondary imaging technique at 10 kv accelerated voltage. Electron provide a 3D image of the scanned object. The SEM study gives an idea regarding the surface view of an object how it looks, its texture, the shape and size of the particlesthat make that object.

3. Results and Discussion

3.1 Evaluation of Powder Blend

The angle of repose of all the preparations was noted in the range of 25.01° to 32.25°.While, the values of Hausner's ratio were found from 1.087 to 1.252. The formulation having Hausner's ratio of 1.25 shows good flow properties. The compressibility index was measured between 8 % to 22 % for all formulations. The value of the compressibility index between 12 percent to 20 percent shows good compressibility, determines that powder blend is in an acceptable range.

3.2 Evaluation of Matrix Tablets

Results in hardness, friability, uniformity in weight and content uniformity are indicated in

Table and were found to be well within the limits (USP).

3.3 In Vitro Buoyancy Studies

3.3.1 Buoyancy Lag Time

In vitro buoyancy lag time of all the (preliminary & optimized formulations) was investigatedand found that a formulation containing HPMC K15 showed best buoyancy lag time less than one minute. While all other formulations containing combination of HPMC K15+Ethylcellulose, HPMC K15+Eudragit RS100 showed buoyancy lag time less thanone minute. Formulations RSFTIII, RSFTVI and RSFTIX showed total buoyancy lag time for 10 hours.

3.3.2 Matrix Integrity

Results for the matrix integrity are as shown in Table 5, formulations RSFTIII, RSFTVI and RSFTIX having better matrix integrity other than all formulations. Tablet formulations manufactured with HPMC K15 15%, 20%, 25% disintegratewithin one hour and failed matrix integrity test. While, formulations (i.e., VI, VII, VIII, IX) containing a polymer Ethocel concentration 20%, 25% and Eudragit RS100 concentration 15%, 20%, 25% and passed the matrix integrity test but failed to float respectively. The formulations (i.e., RSFTI, RSFTII, RSFTIII, RSFTIV, RSFTVI, and RSFTIX) showed good floating lag time and formulations (i.e., RSFTIII, RSFTVI, and RSFTIX) remained buoyant for 10hrs.When formulated tablets come in contact with the dissolution medium (0.1N HCl) having gastric pH 1.2 containing gas producing agents Sodium bicarbonate (16.67%) and Citric Acid anhydrous (6.67%) that induced CO_2generation. The generatedCO_2 is entrapped into the gel-matrix that is formed by the water uptake of the polymer, thus causing to decrease the tablet's density and as a result bylowering density of the tablet becomes buoyant.

3.3.3 Swelling Study

Swelling index of optimized formulations (RSFTIII, RSFTVI, and RSFTIX) was calculated Percentage of water uptakeshowed that as polymer concentration increases there also increases water uptake.

3.4 In Vitro Drug Release Studies

By *in vitro* drug release profile studies, it can be concluded that tablet formulations (VII, VIII, IX) with polymer Eudragit RS 100 concentration15%, 20%, 25%, showed good matrix integrity but poor property of floating.These formulations floated after 1.5hrs and remained buoyant for 10hrs.Thus, it was assumed that Eudragit RS 100 was considered the best polymer for sustained release matrix tablet not for the effervescent floating matrix tablet. It was also concluded that that increase in the concentration of HPMC K15 showed good control in drug release as well as floating properties also improved as formulation (RSFTIII) that showed better floating properties and remained buoyant for 10hr. Therefore HPMC K15 at higher concentration was considered to be ideal polymer for formulating floating tablets of risperidone. Tablets formulated with Ethylcellulose showed poor

floating properties therefore it was not considered in formulating floating tablets. Combination of HPMC K15 &Eudragit RS 100 and HPMC K15 &Ethylcellulose was formulated to investigate the floating properties and buoyancy studies. Combination of HPMC K15 50%, 55%, 60% and Ethylcellulose 15 % (RSFTIV, RSFTV, and RSFTVI) showed good floating properties but formulation (RSFTIV, RSFTV) failed to hold drug and showed poor matrix integrity and disintegrated within 1hr.

Combination of HPMC K15 50%, 55%, 60% and Eudragit RS 100 15% (RSFTVII, RSFTVIII, RSFTIX) also showed good floating properties but formulations (RSFTVII, RSFTVIII) showed poor matrix integrity and disintegrated within 1h.Combination of HPMC K15 60% & Ethylcellulose15% (RSFTVI) and HPMC K15 60% &Eudragit RS100 15% (RSFTIX) showed better floating properties and remained buoyant for 10hrs.

3.5. Kinetic Modeling of Drug Release

To investigate the mechanism of drug release from formulating dosage forms, the data was put on various drug release models such as zero order kinetics model, first order kinetics model, Hixson-Crowell kinetics model, Higuchi kinetics model and KorsemeyerPeppaskinetics model. Values of correlation coefficient 'R2' for zero order kinetics was calculated and found between (0.9898 to 0.9968). While, the value of correlation coefficient 'R^2' of formulation RSFTVI (0.9968) indicated good fit of Zero order model refers to the process of constant drug release from a drug delivery system. While, the drug release data were fitted to KorsmeyerPeppas equation, the values of slope 'n' (0.361 to 0.522) indicated that the drug release for RSFTIII & RSFT IX was by fickian mechanism and for RSFTVI was by anomalous. As formulation RSFTVI containing (HPMC K14 &Ethylcellulose) results releasing (99.7%) of the drug in 10hrs. With buoyancy lag time of 7 Sec and total buoyancy time of (10 hrs.) has been suggested an ideal preparation. While morphological characterization by Scanning electron microscopic study moreover validated that swelling and diffusion mechanisms to are involved mainly in drug release from the preparation RSFTVI.

Table 8. Release-kinetics parameter of optimized floating tablets of risperidone.

Dissolution medium =pH1.2												
Formulation	**Zero order**		**First order**		**Higuchi**		**Korsemeyer-peppas**			**Hixson Crowell**		**Mechanism**
RSFTIII	k	R^2	k	R^2	k	R^2	k	R^2	n	R^2	k	Fickian
	33.95	0.9898	0.1696	0.823	0.0988	0.983	2.64	0.982	0.402	0.919	4.365	
RSFTVI	23.05	0.9968	0.3682	0.882	0.058	0.983	3.3998	0.980	0.522	0.9579	4.617	Anamolous
RSFTIX	35.67	0.9915	0.0426	0.885	0.138	0.972	2.4264	0.966	0.361	0.925	4.25	Fickian

3.6 FTIR Spectroscopic Analysis

In order to confirm interactions, samples were analyzed by FTIR spectroscopic technique. Figure 1,2,3,4 show pure drug's spectra, (Drug + HPMC K15), (Drug + Eudragit RS100+HPMC K15), (Drug + EC+HPMC K15) respectively. The FTIR pure drug's spectra having peak at 2939.08 cm^{-1} because of the stretching of (-OH) groups (Carboxylic Acid), while, peak at 2939.08 cm^{-1} also showing the (–C-H) stretching vibration. The peak at 1642.33 cm^{-1} indicated (C=C) stretching's vibrations due to the presence of aromatic ring/alkene which is completely substituted , peaks at 1531.52 cm^{-1} and 1349.33 cm^{-1} could be suggested to ($–CH_{2)}$ scissoring and (–OH) bending vibration, respectively, peak at 1150 cm^{-1} indicated the presence of (–CH-OH) group. The peak at 1128 cm^{-1}indicated (–CH-O-CH-) stretching.

3.7 Scanning Electron Microscopy (SEM)

SEM was performed before and after dissolution to take SEMimages of the tablet to elucidate morphological characterizationof tablet's texture. As shown in the fig. 5, we see no distinct perforations, channels and troughs. The process of dissolution progress from the outer boundary of the matrix which gradually progress towards the central core.The drug diffuses out from the matrix as contacting with dissolution medium. As shown in the fig. 5, we see no distinct perforations, channels and troughs. The process of dissolution progress from the outer boundary of the matrix which gradually progress towards the central core. The drug diffuses out from the matrix as contacting with dissolution medium. As shown in the figure. 6, we see distinct troughs in the swelled polymer through which the drug diffused out to the surrounding medium which describes that diffusion is the main controlling mechanism overall.

3.8 Testing Dissolution Equivalency

Dissolution equivalency is computed by the estimation of similarity factor analysis as well as by difference factor analysis. The optimized formulation RSFTVI was considered as test formulation and other both optimized formulations RSFTIII & RSFTIX were considered as reference formulation .The difference factor analysis (f1) and similarity factor analysis (f2) between the formulation RSFTIII and RSFTVI & formulation RSFTIX and RSFTVI showed f1 factor (f1=9), f2 factor (f2=58) & (f1=12) (f2=55)and f1valuesare less than 15 and f2 values are greater than 50 respectively, which confirms the similarity in release of both the test and reference formulations.

3.9. In Vivo Evaluation

In vivo evaluation was done and radiographic x-ray is as shown in fig. 12 after 1 and 4 hours respectively.*The tablets remain floating in the stomach for over (4hrs.) in human volunteers.*

4. Conclusion

Risperidone floating matrix tablets were formulated by blending drug, HPMC K15, Ethylcellulose, EudragitRS100 and gas generating agent, and fillers by wet granulation and IPA was used as granulating solution. The matrix tablets of risperidone swelled when came in contact with the aqueous medium. Tablets formulated with Eudragit RS100, Ethylcellulose failed to float, but showed better matrix of required strength. The formulations RSFTIII

containing HPMC K15 showed good floating abilities.The combination of HPMC K15 with Eudragit RS 100 &Ethylcellulose containing formulations RSFTVI and RSFTIX showed better matrix integrity. It was concluded that formulation RSFTIII containing HPMC K15 gave the best *in vitro* release of 98.44% in (10 hrs.) and best fit to zero order release kinetics. *In vivo* evaluation, by X-ray technique showed that the tablet was retained in the stomach for 4 hours.

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