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Determining the release kinetics of risperidone controlled release matrices to treat schizophrenia

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Abstract: Risperidone is an atypical antipsychotic agent clinically used to treat schizophrenia, bipolar diseases, and autism. Usually, the frequency of doses is twice daily. In the present study, risperidone controlled release matrices formulated using hydrophilic and hydrophobic polymers. The tablets were prepared by direct compression. The pre-compression and post-compression properties were assessed, along with swelling studies. The morphology of particles observed using scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FT-IR). The stability study on the drug was performed using thermal gravimetric analysis (TGA) and differential thermal analysis (DTA). The optimized formulation was prepared with the help of hydrophilic polymer K100M (40% ratio). Furthermore, release kinetics had investigated. The release pattern of optimized formulation FT5 fitted best to zero-order kinetics and showed excellent release characteristics. The model-independent approach had been used, formulations FT6 and FT8 showed resemblance with FT5 in all three media, respectively. The once daily formulation of risperidone could be beneficial for schizophrenia patients and their caregivers and will improve patient compliance.

Keywords: Matrix, hydrophilic, stability, SEM, TGA, zero-order kinetics.

INTRODUCTION

Risperidone, an antipsychotic agent, is clinically utilized to treat Schizophrenia, bipolar diseases, and autism (Coughlin. *et al*., 2016). It blocks serotonin (5-HT2) and dopamine (D2) receptors Risperidone is considered soluble freely in methylene chloride, whereas particularly soluble in water (2.16 mg/L at 25°C) (Sweetman, 2002; Katzung & Trevor, 2017). It usually seems inconvenient to follow the dosage regimen easily due to memory problems; hence it has been felt that a single tablet for 24 hours could be beneficial. Elevated plasma levels of risperidone may result in serious adverse effects, and the controlled release formulation has been designed in a manner that regulates plasma levels of the drug between minimum effective and maximum safe concentration (Kohrs *et al*., 2019; Davoodi *et al*., 2018; Leon *et al*., 2007). It chiefly metabolizes in the liver and Cytochrome P450 catalyzes the drug metabolism (Grant and Fitton, 1994; Mannens *et al*., 1993). The treatment doses for schizophrenia are 2 to 8 mg daily in repeated doses.

The current innovations in pharmaceutical dosage forms are for convenience of patients facing problems due to repeated doses (Kumar *et al*., 2018). Controlled-release tablets could maintain the appropriate drug concentration in plasma with reduced dosing frequency and avoiding chances of forgotten doses (Aulton and Taylor, 2017).

The objective is to design orally modified tablets of risperidone, higher viscosity grade and loadings of polymers have used that slow down the drug release after gel formation followed by erosion (Patrick and martin, 2017; Agarwal and semimul, 2019). Dissolution kinetics had been observed in different pH media, the release profile was calculated by applying kinetic models. D. D solver software used to establish the release pattern (O'hara *et al*., 1998; Shah *et al*., 1998).

MATERIALS AND METHODS

Chemicals

Risperidone was gifted from Medisure Laboratories Pakistan, Methocel® (K15M and K100M) (Colorcon, England), Kollidon SR (BASF, Germany), magnesium stearate (Dow, USA),Avicel PH 101 (FMC, USA), acetonitrile, methanol, excipients, and chemicals were of best analytical grade and bought from the authorized dealer (Merck, Darmstadt, Germany).

Pre formulation assessments of trial formulations

Micromeritic properties of powder blends were determined by using a measuring cylinder as per USP method (USP35-NF30, 2012a).

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Tablet formulation

The weight of all ingredients was carefully noted and sieved through a forty-mesh size sieve. Active components and excipients were mixed for 10 to 15 minutes in a polybag. Magnesium stearate was mixed, and then the resultant powder mix was directly compressed on a single punch compression machine (Zhengzhou, China) in 100 mg tablet (table 1).

Post compression analysis of Risperidone matrices

Physical parameters were analyzed, variation in weight was checked on an analytical balance (Mettler Toledo, England) Tolerance limits were according to British Pharmacopeia (B.P, 2013). Thickness was evaluated with Vernier Caliper (Digital China). Hardness was assessed on a Hardness tester (Erweka, Germany). Friability was analyzed by Friabilator (Erweka, Germany) and calculated according to the specifications of US Pharmacopeia (USP35-NF30, 2012a). A disintegration test was performed on Basket rack assembly (Erweka disintegration assembly Germany).

STATISTICAL ANALYSIS

Statistical analysis (Mean ± S.D) of the formulations was performed on M.S. Excel® version 2010.

% Moisture uptake

The ability of moisture uptake was also investigated. 250 mL of water (de-ionized) was taken in 3 separate beakers; the temperature was kept at 25ºC after 10 hours (Joshi, 2011; Cao *et al*., 2005). The percentage of moisture uptake (%) was calculated with the given formula,

$$\%\,S = \frac{W_t - W_o}{W_o} \times 100 \quad (1)$$

Where S represents the % of moisture uptake, W_t and W_o were the initial and final weights.

Fourier transform infrared (FT-IR) spectroscopy

Fourier transform infrared (FT-IR) spectroscopy was performed on Thermo Scientific FT-IR Spectrometer (Germany) by applying ATR crystal technique.

Thermal gravimetric analysis and differential scanning calorimetry (TGA-DSC)

The thermal stability of Risperidone was assessed using SDT 650 simultaneous TGA-DSC thermal analyzer. About four mg of sample was taken in the sample holder. In contrast, an empty aluminum reference holder was taken as standard. Analysis recorded on the temperature range of 20 to 600ºC, the rate was 10ºC/min. The flow rate was 99.98 mL/min in the active nitrogen atmosphere.

Scanning electron microscopy (SEM)

Morphological characteristics of optimized formulation were analyzed using a scanning electron microscope (SEM) (JSM-6380A, Jeol, Japan) at 10 kV.

Dissolution study

The dissolution test was performed in a dissolution tester (Erweka, Germany) with a 50 rpm paddle speed. According to USP guidelines (USP35-NF30, 2012b), CR matrices were assessed at different pH (1.2, 4.5, and 6.8) for drug release kinetic studies. Afterward, tablets were analyzed for risperidone content with a UV–visible spectrophotometer (UV-1800, Shimadzu, Japan) set at λmax 280 nm.

Assay

A reported HPLC method (Dedania *et al*., 2011) was adapted for the assay of tablets with a few modifications. The system comprised of HPLC Pump (LC-10 AT VP, Shimadzu), a model of UV Detector (SPD-10AVP, Shimadzu) was used. Chromatographic elution was achieved using HPLC Column (Bondapak C-18, 4.6x250 mm, Germany) at ambient temperature and the wavelength of 280 nm. The mobile phase composition was methanol and acetonitrile in a ratio of (80:20), and a flow rate was set at 1 mL/min.

Stability evaluations

Stability testing was performed at accelerated conditions (40±2 °C/75±5% RH). ICH guidelines (ICH, 2003). A stability chamber (Binder, Germany) at accelerated conditions was used for storage of samples and evaluated at 0, 3, and 6 months according to USP (USP35-NF30, 2012b). Furthermore, the vetting of dissolution kinetics of matrices was conducted in the similar media.

Model dependent analysis

Zero-order model: $$Q_t = K_o t \quad (2)$$

K_o is a zero-order rate constant, the time (hrs) is t and the quantity released drug is denoted by Q_t.

First-order model: $$\mathrm{Log}Q_t = \log Q_o - k_t / 2.303 \quad (3)$$

Qt and Qo are quantity of release drug and initial concentration of the drug, respectively, while kt denotes rate constant of the first order.

Korsmeyer's model: $$M_t / M_\infty = Kt^n \quad (4)$$

K is indicative of Korsmeyer's rate constant and release exponent, obtained after calculating the slope of a straight line, which specifies the release pattern (Hixson and Crowell, 1931). Matrices which are cylindrical in shape, exponent value of 0.45 is characteristic of Fickian release (case I), the value of exponent should lie within >0.45 to <0.89 (Korsmeyer *et al*., 1983).

Higuchi's model: $$Q = kt^{1/2} \quad (5)$$

k indicates constant for release rate, t is the time in hours. The release rate correlates to the reciprocal of the time's square root (Bourne, 2002).

Hixson–Crowell model: $Q_o^{1/3} - Q_t^{1/3} = K_{HC} \times t$ (6)

*K*HC denoted the rate constant of Hixson-Crowell. Qo, Qt represents drug concentration (initial) and quantity of released drug respectively, t indicated the time.

Model-independent analysis

Similarity factor f_2: Similarity factor is the logarithmic corresponding square root conversion of summation of squared error and an assessment of resemblance in % drug dissolved between both curves:

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{N}\sum\left(R_i - T_i\right)^2\right)\right]^{0.5}\right\} \times 100 \quad (7)$$

If the calculated value falls between 50 to100, then the profiles are regarded alike, while for lesser values of f2, the profiles are considered dissimilar (Costa and Sousa Lobo, 2001). DD-solver (MS Excel) was used for the estimation of regression coefficients and release rate constants.

RESULTS

The pre compression properties of all formulation blends were estimated (USP35-NF30, 2012b) (table. 2).

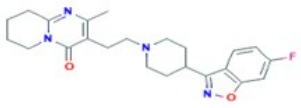

Fig. 1: Risperidone

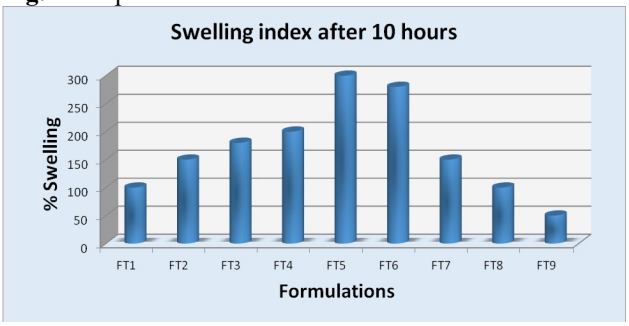

Fig. 2: % Swelling of formulated tablets

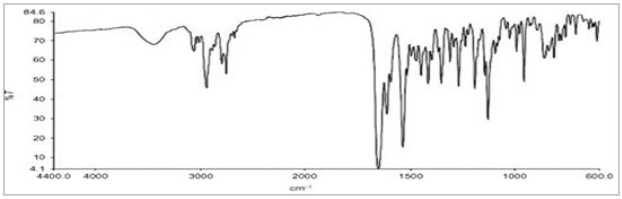

Fig. 3: FTIR spectrum of optimized formulation FT5

Post compression analysis of risperidone tablets

Risperidone tablets were analyzed for physical parameters, dissolution, and assay (table 3).

%Moisture Uptake

The results showed that hydrophilic polymer has more wettability than hydrophobic polymer, tablets containing hydroxypropyl methylcellulose (HPMC) showed more swelling than tablets with kollidon due to its hydrophobic nature (fig. 2).

Fourier Transform Infrared (FT-IR) spectroscopy

The Fourier transform infrared (FT-IR) spectra showed all characteristic peaks of risperidone (fig. 3).

Thermal gravimetric analysis and differential scanning calorimetry (TGA-DSC)

The thermal degradation pattern of risperidone was determined by TGA-DSC. The thermogram was shown in figure 4, which depicted a sharp melting point near 300°C at which major weight loss occurs. The increase in weight above 450°C can be due to the oxidation reaction. Decomposition is confirmed by heat flow curve through endothermic peak appeared at 75-150oC indicating that the material was crystalline in the beginning. The decomposition of the sample occurs at a temperature above 220°C (fig. 4).

Scanning electron microscopy (SEM)

External morphology and texture were displayed in SEM images which showed a rough and irregular surface of particles (fig. 5).

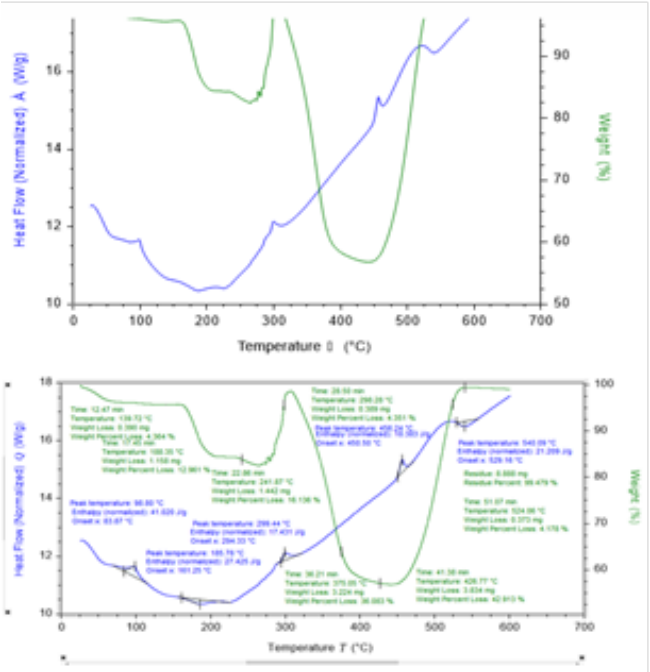

Fig. 4: TGA of FT5 optimized formulation

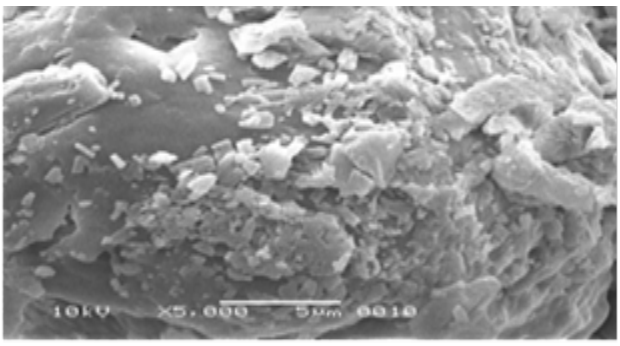

Fig. 5: SEM of FT5 optimized formulation

Table 1: Risperidone matrix formulations

Code	HPMC (mg)	Kollidone SR (mg)	Drug (mg)	Avicel pH101 (mg)	Mg stearate (mg)	Total (mg)
FT1	30	-	20	48	2	100
FT2	40	-	20	38	2	100
FT3	50	-	20	28	2	100
FT4	30	-	20	48	2	100
FT5	40	-	20	38	2	100
FT6	50	-	20	28	2	100
FT7	-	30	20	48	2	100
FT8	-	40	20	38	2	100
FT9	-	50	20	28	2	100

*Formulations FT1, FT2 and FT3 contained K15M 30, 40 and 50%, respectively, formulations FT4, FT5 and FT6 contained K100M 30, 40 and 50%, respectively and FT7. FT8 and FT9 contained Kollidon SR 30, 40 and 50%, respectively

Table 2: Pre-compression properties of HPMC containing formulation powder blends

Formulation Code	Mass (g)	Bulk volume (mL)	Tapped volume (mL)	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's ratio	Carr's index %	Angle of repose	Flow Characteristics (USP- 35, NF-30)
FT1	10	17	16	0.58	0.62	0.94	6.45	31.22	Good
FT2	10	19	15	0.52	0.66	1.26	21.21	32.46	Good
FT3	10	18	16	0.55	0.62	1.12	11.29	31.43	Good
FT4	10	24	16	0.41	0.62	1.51	33.87	47.79	Poor
FT5	10	19	17	0.52	0.58	1.11	10.34	29.76	Excellent
FT6	10	18	14	0.55	0.71	1.29	6.45	31.67	Good
FT7	10	23	17	0.43	0.58	1.34	25.86	43.29	Poor
FT8	10	24	20	0.41	0.5	1.21	18.00	37.28	Fair
FT9	10	23	20	0.43	0.5	0.86	14.00	41.26	Fair

Table 3: Physical parameters and assay results of risperidone controlled release tablets

S. No	Formulation	Weight (mg) Mean + S.D (n=20)	Hardness (Kg) Mean + S.D (n=20)	Thickness (mm) Mean + S.D (n=20)	Friability (%) (n=10)	Disintegration time (hours)	Assay
1	FT1	98.75 ± 4.57	6.42± 0.98	3.01±0.11	0.82	5.27	95.38
2	FT2	100.16 ± 1.89	7.96 ± 0.89	3.12±0.13	0.91	4.54	97.85
3	FT3	98.67 ± 6.55	8.44± 1.61	3.01±0.14	0.72	5.68	98.12
4	FT4	100.6 ± 3.70	7.53± 1.03	3.02±0.12	0.68	3.97	96.18
5	FT5	102.68 ± 4.59	9.18± 0.77	3.10±0.10	0.71	5.69	98.67
6	FT6	100.15 ± 3.90	6.62± 1.01	3.22±0.13	0.96	4.34	95.85
7	FT7	101.63 ± 2.94	8.21±0.86	3.13±0.14	0.78	4.75	95.32
8	FT8	101.05 ± 2.78	7.35±1.19	3.21±0.08	0.57	5.85	96.89
9	FT9	104.2 ± 3.80	7.30 ±0.98	3.18±0.17	0.98	5.32	97.71

Table 4: Model dependent data of risperidone matrices

Matrix Code	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-crowell	
	r^2	$K_0(h^{-1})$	r^2	$K_1(h^{-1})$	r^2	$K_H(h^{-1/2})$	r^2	N	$K_{kp}(h^{-n})$	r^2	$K_{HC}(h^{-1/3})$
In 0.1N HCl											
FT3	0.990	13.006	0.979	0.251	0.991	30.601	0.979	0.558	27.940	0.992	0.069
FT5	0.997	10.299	0.969	0.159	0.972	22.901	0.988	0.763	14.902	0.983	0.046
FT6	0.990	7.987	0.977	0.107	0.971	17.892	0.986	0.749	11.941	0.986	0.029
FT8	0.986	12.399	0.980	0.181	0.973	27.299	0.987	0.681	21.211	0.986	0.051
In Buffer pH 4.5											
FT3	0.995	13.401	0.980	0.257	0.985	31.300	0.987	0.523	32.087	0.982	0.067
FT5	0.997	10.919	0.959	0.170	0.965	25.818	0.987	0.702	17.772	0.960	0.051
FT6	0.978	8.410	0.964	0.125	0.977	18.157	0.974	0.708	13.314	0.974	0.033
FT8	0.984	11.700	0.973	0.186	0.969	27.148	0.992	0.612	21.487	0.974	0.047
In Buffer pH 6.8											
FT3	0.984	13.187	0.990	0.244	0.989	28.014	0.988	0.600	26.100	0.980	0.059
FT5	0.997	10.087	0.966	0.148	0.967	25.125	0.991	0.819	14.875	0.983	0.052
FT6	0.983	7.879	0.981	0.103	0.971	78.035	0.979	0.810	11.632	0.981	0.031
FT8	0.988	12.182	0.978	0.169	0.979	26.006	0.980	0.688	19.113	0.989	0.054

Table 5: Similarity F2 factor evaluation of risperidone matrices

	pH1.2	pH 4.5	pH 6.8	
Methocel K15M				
F5 and F3	19.71	20.57	22.34	Dissimilar
K100M				
F5 and F6	59.82	58.43	61.45	Similar
Kollidon SR				
F5 and F8	57.39	58.29	58.13	Similar

Table 6: Stability data risperidone of matrices

Study period	Test	F5	F6	F8
0 Month	Breaking strength (kg)	9.04±1.21	8.24± 1.45	8.22±1.78
	Friability	0.44	0.68	0.77
	Disintegration (hrs)	7.23	6.04	6.17
	Dissolution %	99.51	98.83	97.87
	Assay %	98.87	98.08	98.14
3 Months	Breaking strength(kg)	8.77±1.55	7.10±1.97	6.96±3.91
	Friability	0.66	0.89	0.91
	Disintegration(hrs)	6.31	5.69	4.89
	Dissolution %	98.68	97.17	97.10
	Assay %	98.11	97.65	97.61
6 Months	Breaking strength(kg)	8.51±0.55	6.88 ±2.03	6.11±1.97
	Friability	0.83	0.96	0.97
	Disintegration (hrs)	6.09	5.13	4.76
	Dissolution %	98.23	97.43	96.43
	Assay %	98.02	97.16	97.01

Drug release kinetics

The release pattern of all formulations shown in figures 6 to 8. FT5 (optimized formulation) released about 80% of the drug released within twelve hours, while 98-100% in twenty-four hours.

Model dependent assessment

The model formulations FT1 to FT9 were vetted for drug release, and findings are represented in figures 6 to 8 and table 4. The drug release exponent and linearity of the curve were established to determine the most suitable model. Formulated tablets FT5, FT6, and FT8 best followed zero-order kinetics (table 4).

The diffusional coefficients achieved using Korsmeyer's equation have lied in a range of 0.45 and 0.89 for F5, F6, F8. The results illustrated that formulation FT5 sustained the drug release. The drug release pattern was not significantly different in all three media (figs. 6-8).

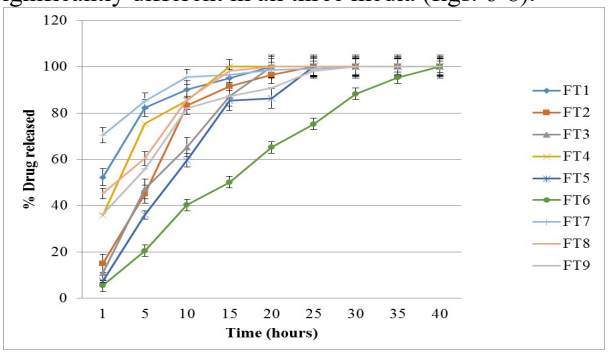

Fig. 6: Drug release profiles of FT1, FT2, FT3, FT4, FT5, FT6, FT7, FT8 and FT9 in 0.1 N HCl

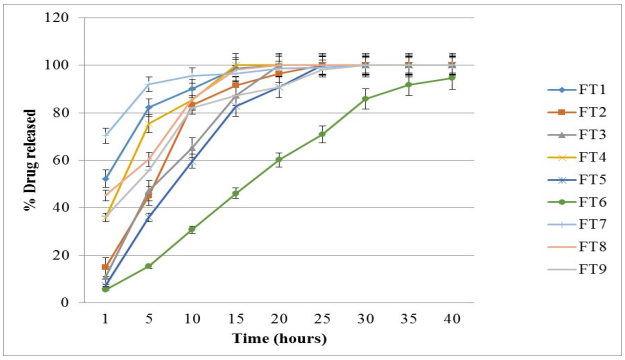

Fig. 7: Drug release profiles of FT1, FT2, FT3, FT4, FT5, FT6, FT7, FT8 and FT9 in 4.5 pH

Model-independent analysis

A model-independent approach was employed to estimate the similarity factor f2 by utilizing DD-solver. The drug release profiles of FT5, FT6, and FT8 were evaluated in comparison with each other. The f2 values of FT5, FT6, and FT8 had resemblance in dissolution patterns (table 5).

Assay

A reported HPLC method (Dedania *et al*., 2011) was used for the assay. All the formulations displayed assay results within USP specified limits.

Analysis of stability parameters

Accelerated storage conditions, 40±2°C/75±5% RH, did not affect markedly the content of the drug, and physical parameters and appearance of the CR matrix. It was

predicted that matrix tablets F5, F6, and F8 might have good sustainability (table 6).

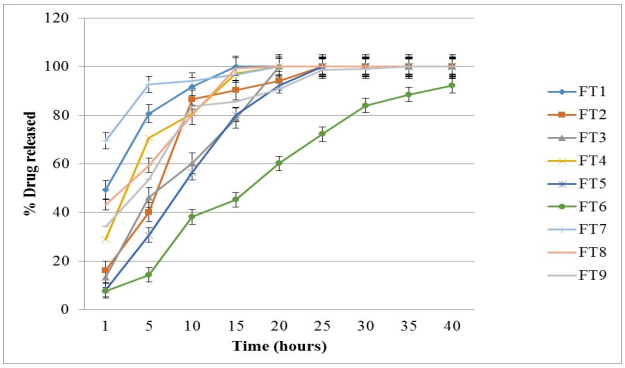

Fig. 8: Drug release profiles of FT1, FT2, FT3, FT4, FT5, FT6, FT7, FT8 and FT9 in 6.8 pH

DISCUSSION

Drug regimen for an antipsychotic drug usually interrupted due to missed doses, resulting in complications and discrepancies (Weiden *et al*., 2004), which paved the way for the need to manufacture once-daily formulation of risperidone. The widely used release-retarding polymers methocel and kollidon SR were used (Thombre G, 2019; Svarstad *et al*., 2001).

The polymer hydrated upon contact with dissolution medium ensued by gel formation and swelling. Furthermore, channels formed in hydrated tablets, which resulted in slow diffusion and release. Ideal release kinetics were exhibited by FT5 K100M (40%). More or less similar profiles were noticed for FT6 and FT8, which released about 55 to 60% drug in 4 hours, 80 to 82% in 8 hours, and 95- 100% in 20 hours. However, FT6 shown a slightly more slow rate of release and gave 60% release in 24 hours. El-Masry., reported similar results with controlled release matrix of etamsylate (El-Masry *et al*., 2020; Ummaheshwari and Jain, 2018; Kamboj *et al*., 2017; Raghuvanshi and Pathak, 2014; Shah *et al*., 2008). Almost the same results had observed for tablets in phosphate buffer (pH 6.8) followed zero order (Arévalo *et al*., 2019; Klančar *et al*., 2015; Klančar *et al*., 2012; Klančar *et al*., 2013; Wang and Shmeis, 2006). Ghori, presented results of hypromellose matrices and claimed similar outcomes (Ghori *et al*., 2014). Stability studies have shown that FT5 was stable at both prescribed conditions (FDA, 1997; ICH, 2005).

CONCLUSION

Optimized formulation of risperidone met required specifications. Release kinetics, revealed that optimized tablet obeyed zero-order kinetics. Complete drug was released within twenty-four hours. The optimized formulation was produced with the help of HPMC K100M (40% ratio). Many doses in a day are inconvenient for patient; the once-daily formulation of risperidone is especially beneficial for schizophrenia patients suffering from loss of memory.

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