FORMULATION AND EVALUATION OF ORODISPERSIBLE FILM OF FLUOXETINE HYDROCHLORIDE

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ABSTRACT

Oral dispersible film of Fluoxetine hydrochloride was formulated and evaluated as a drug delivery system. Preformulation studies were performed. The maximum absorbance of the pure drug Fluoxetine HCl was found to be 226 nm when sample scanned fro 200-400nm. Drug showed good linearity with the regression of co-efficient (R^2) of 0.998 and the equation for this line found 0.049x-0.015. Fast dissolving film was found Thin, smooth and transparent. The *in-vitro* disintegration time of the films prepared with final formulation shows disintegration time 23 ± 2.0, 24 ± 1.2, 26 ± 1.0, 28 ± 1.4, 29 ± 2.2 and 33 ± 3.0 second for F-1 to F-6 batches. Tensile Strength of film was between 4.40 ± 0.064 to 5.40 ± 0.034 (gm/mm^2), film Elongation was 14.21 ± 0.21 to 26.81 ± 0.42 %. Surface pH for all formulation F-1 to F-6 was found in the range of 6.5 to 6.8. Surface pH of all films was within the range of salivary pH. Drug content for all formulation was found to be in the range of 91 % to 98.40% which shows uniformity of drug content in all formulation. *In-vitro* release for fast dissolving film of Fluoxetine HCl was found rapid about 55% of drug was release in 5 min and total 93.37% in 30min. *In vitro* release data fitted into various kinetic models suggest that the best fit model was first order model with R^2 value 0.935. No significant change was observed in drug content and disintegration time at room temperature and as well as on accelerated stability studies at 40°C ± 2°C/75 % RH ± 5% RH. Hence formulation F-3 was found to be stable for 90days. It was concluded that the prepared film of Fluoxetine HCl was a satisfactory attempt to formulate oral dispersible film and may also prove to be a potential candidate for safe and effective oral dispersible drug delivery.

KEYWORDS: Oral dispersible film, Fluoxetine, FT-IR spectroscopy, Fast dissolving film, ICH

INTRODUCTION

The recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs[1]. Out of those, drug delivery system being very eminent among pediatrics and geriatrics is orally disintegrating films (Oral Dispersible Film)[2]. This drug delivery system has numerous advantages over conventional fast disintegrating tablets as they can be used for various diseases and are taken without water due to their ability to disintegrate within a few seconds releasing medication in mouth. Different drugs can be incorporated in the film[3,4]. Various approaches are employed for formulating oral dispersible film and among which solvent casting and spraying methods are frequently used[5]. Generally, hydrophilic polymers along with other excipients are used for preparing oral dispersible film which allows films to disintegrate quickly releasing incorporated active pharmaceutical ingredient (API) within seconds[6]. Orally disintegrating films have potential for business and market exploitation because of their myriad of benefits over orally disintegrating tablets[7]. Fast dissolving oral films are found to be good enough for a particular need in many situations like allergic conditions, cold and cough, nausea, sore throat, pain, mouth ulcers, CNS disorders and CVS disorders[8].

The rationale behind the use of Fluoxetine hydrochloride is that the use of this drug in the treatment of panic attacks, obsessive compulsive disorder etc needs the fast action of the drug for the patients which can calm them quickly which can be accomplished by the use of the oral dispersible film. Therefore keeping the need of fast release of drug, oral dispersible film has been thought as a better drug delivery system to comply the patient's need.

MATERIALS AND METHOD

Fluoxetine hydrochloride was obtained from Yarrow Chem., Mumbai as gift. HPMC E15 purchased from Colorcon Ltd. Goa, PVP and Citric Acid from Loba Chemicals, Mumbai, and PEG-400 from S.D Fine Chemicals Ltd, Mumbai. All reagents used were A.R. grade.

Preformulation Studies: Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients.

Formulation of Oral Dispersible Films (ODF)

The solvent casting method with necessary modifications was used for the development of ODF based on the composition given in Table. The weighed quantity of Hydroxy Propyl Methyl Cellulose (HPMC) or Poly Vinyl Pyrrolidone (PVP) was dissolved in a one-by-the–fourth volume of distilled water taken in a beaker. The solution was continuously stirred using a magnetic stirrer at 600 rpm. Accurate amount Fluoxetine HCl was dissolved in a sufficient volume of distilled water and vortex. The drug solution was added drop by drop to the polymer solution, which was kept under continuous stirring. In a separate beaker, weighed quantity of Crosspovidone (CP), Citric Acid (CA), Poly ethylene Glycol (PEG–400), and saccharin sodium was dissolved in the remaining volume of distilled water, which was stirred for 30 m using a magnetic stirrer at 600 rpm. The resultant solution was added to the drug– polymer blend, followed by the addition of Vanilla flavor and continued stirring for the next 1 hr. The solution was kept aside and allowed for the removal of any entrapped air bubbles. The solution was poured into a previously designed glass mould of 8cm x 5cm (W x L) dimension and allowed for drying at room temperature ($30^{O} \pm 2\,^{O}C$) for the next 24–48 hr. The dried film was cut into strips of 2cm X 2cm size, wrapped in aluminium foil, and stored in desiccators until used for further studies. A similar procedure was followed for ODF based on PVA and ODF without CP.

Table No. 4: Formulation of Oral Dispersible Film

Ingradients	F-1	F-2	F-3	F-4	F-5	F-6
Fluoxetine HCl (mg)	100	100	100	100	100	100
HPMC E15(mg)	200	250	300	350	400	450
PVP (mg)	200	200	200	200	200	200
Citric Acid (mg)	100	100	100	100	100	100
Crospovidone (% w/v)	-	4	8	-	4	8
PEG-400 (ml)	0.40	0.40	0.40	0.40	0.40	0.40
Sod. Saccharin (mg)	100	100	100	100	100	100
Vanilla flavor (mg)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled Water (mg)	10	10	10	10	10	10

RESULTS AND DISCUSSION

Preformulation studies were performed. Fluoxetine HCl was a white amorphous white color, Odorless, Crystalline powder with bitter in taste. Fluoxetine HCl was found that freely soluble in 0.1 N HCl, soluble in methanol, ethanol, chloroform, distilled water, 6.8 pH phosphate buffer and 0.1 N NaOH, with the melting point range of 157-160 ^{O}C. The maximum absorbance of the pure drug Fluoxetine HCl was found to be 226 nm when sample scanned fro 200-400nm. From the standard calibration curve, it was observed that the drug obeys Beer's law in the concentration range of 2-12µg/ml in phosphate buffer of pH 6.8. Drug showed good linearity with the regression of co-efficient (R^2) of 0.998 and the equation for this line found 0.049x-0.015 which was used in the calculation of the drug content, as well as in dissolution study.

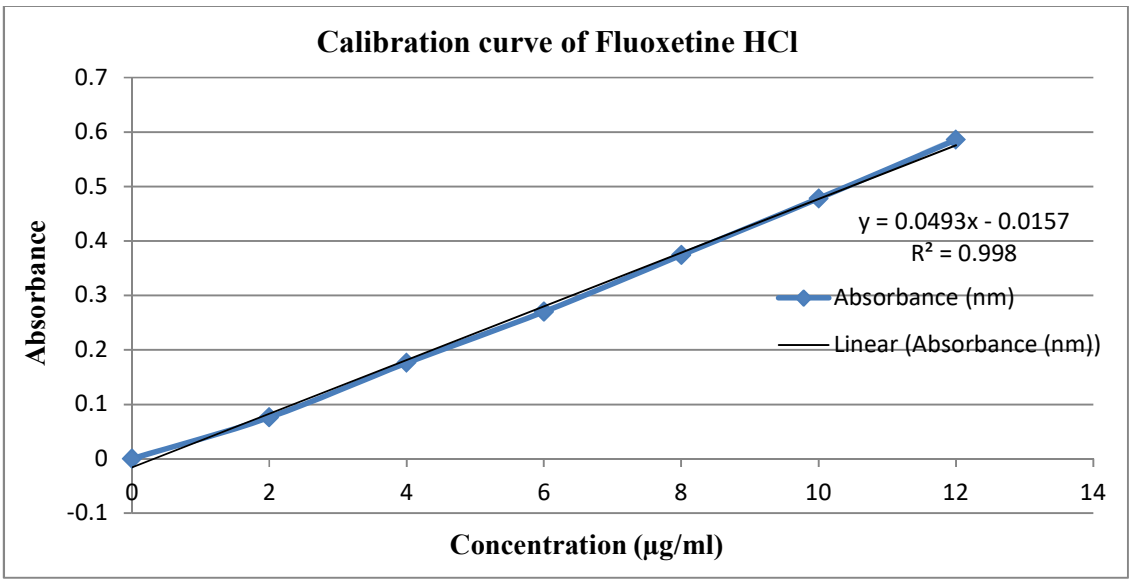

Figure 4: Calibration curve of Fluoxetine HCl at 226nm in phosphate buffer of pH 6.8

The peaks obtained in the FT-IR spectroscopy of Fluoxetine hydrochloride and the mixture of excipients with the drug was matched with the standard values for the compatibility of the drug with excipients and it shows no interaction between them as they are compatible with each other.

Evaluation of fast dissolving films

Physical appearance: This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch. The observation suggests that the films were having Thin, smooth and transparent.

Weight uniformity of films: Orodispersible films of the size 2x2 cm^2 were weighed individually using digital balance and the average weights were calculated. All ODF batches qualified for the % weight variation according to USP pharmacopeial limit of ± 10% for dosage form with 139 mg or less weight. Weight of Films in formulation F-1 to F-6 was about 96 ± 2.36, 122 ± 1.22, 140 ± 0.92, 165 ± 1.02, 176 ± 0.98 and 193 ± 1.62 mg respectively. Film was found uniform in weight.

Thickness of films: The thickness of the films was measured using micro meter screw gauge and the average thickness. The thickness range of the typical film must be within the range of 50 µm-1000 µm. The optimum and homogenous thickness of the film is requisite for its uniform drug distribution, which ultimately has a profound effect on its content uniformity. Uniform drying of ODF is a crucial stage in providing the uniform thickness of the ODF batch. The recorded thickness values were almost uniform in all trials suggesting the homogenous distribution of all ingredients in the ODF. In addition, findings also highlighted the validity of uniform drying in a hot air oven at 45°C. The ODF with higher thickness values contributes toward diminished pliability and consequently low values in folding fortitude evaluation. The average thickness of F-1 to F-6 was found to be 0.53 ± 0.01, 0.67 ± 0.04, 0.78 ± 0.02, 0.92 ± 0.02, 1.06 ± 0.04 and 1.18 ± 0.02 mm respectively. From the above observation it was observe that increased in polymer concentration increases thickness of the film. Similarly increased in plasticizer concentration slightly increases thickness.

Folding endurance of films: A plasticizer is supposed to impart major pliability properties along with main polymers. In this context, plasticizer plays its role by entrapping itself into the polymer matrix and consequently rupturing and weakening the polymer-polymer linkages and augmenting the motility of polymer strands. The folding fortitude of all retrieved ODF trial formulations was within the scale 178 ± 3.1 to 253 ± 2.3. In contrast, the ODF with relatively higher HPMC tended to show diminished flexibility and exhibited lowered folding endurance. There is no authentic, official pharmacopeia value range for folding endurance; hence the ODF with about 250 folding fortitude values were regarded as ODF with good folding endurance attribute.

***In vitro* disintegration time of films:** As European pharmacopeia publishes that ODF must disintegrate as placed in a buccal cavity. However, it does not declare any authentic method and

maximal acceptable time for disintegration. Centre of drug evaluation and research states that the disintegration time range should be within the limits of 0-30 sec, so the same criterion was selected for ODF. PVP was worked as plasticizer as well as the super-disintegrant in a concentration of 100 mg per ODF batch. The PVP performs rapid disintegration by absorbing water through capillary action and expands, ultimately increasing hydrostatic pressure, which is required to disintegrate ODF readily. Notably, the disintegration time ascended with the aggravation of polymer content in the ODF trials. Furthermore, the constant concentration of super-disintegrant in all ODFs was sparse to induce the disintegration in ODF of such high polymer content. Therefore, it can be assumed that the concentration of super-disintegrant must be commensurate with polymer content in ODF, and its higher concentration will lead to faster disintegration. Moreover, high polymer content could also be the cause to seal the capillary pores and ultimately block the influx of liquid into ODF, resulting in delayed disintegration time.

ODF trial batches recorded the disintegration time equal to or less than 30 sec were regarded as the successful ODF in terms of disintegration time characterization. After keen analysis of disintegration time correlated to polymer percentage, it was inferred that ODFs formulated with polymer content revealed themselves with exceptionally short disintegration time up to sec. The recorded data showed that PVP proved itself as a competent super-disintegrant for the ODF formulation, although its efficacy is contingent on incorporating polymer concentration. The *in-vitro* disintegration time of the films prepared with final formulation shows disintegration time 23 ± 2.0, 24 ± 1.2, 26 ± 1.0, 28 ± 1.4, 29 ± 2.2 and 33 ± 3.0 second for F-1 to F-6 batches.

Mechanical Properties: Mechanical properties such as Tensile strength and % Elongation of different formulation were recorded in Table. Classical ODF must be physically robust and pliable. These traits can be interpreted as classical ODF must possess high tensile strength and high percent elongation at rupture and low value of Young's modulus. According to CQA of mechanical properties of ODF, corresponding values should be as tensile strength >2 N/mm^2, % elongation >10%, Young's modulus <550 N/mm^2. Fluoxetine HCl oral film was robust, flexible, and tough. The concentration of incorporated plasticizer has positive effects on tensile strength and % elongation could be due to bonds formation between plasticizer (PVP) and polymer (HPMC), thereby imparting adequate flexibility and fortitude to ODF to endure and resist the rupture. However, it was found that plasticizer concentration has a negative effect on

disintegration time. It is also to be considered that much higher elongation is not desirable because it could generate the problem of elongation at edges while cutting the ODF batches, which could yield inhomogeneous ODFs, and diversify drug load. Therefore, optimal incorporation of appropriate plasticizer concentration holds key importance in the formation of classical ODF with adequate physical attributes.

Table No. 9: Evaluation of Orodispersible films of Fluoxetine HCl

Formulation Code	Physical Appearance	Weight Uniformity (mg)	Thickness of Film (mm)	Folding Endurance of Film	*In-vitro* Disintegration Time (sec)
F-1	Thin, Smooth, Transparent	96 ± 2.36	0.53 ± 0.01	250 ± 1.2	23 ± 2.0
F-2	Thin, Smooth, Transparent	122 ± 1.22	0.67 ± 0.04	243 ± 2.3	24 ± 1.2
F-3	Thin, Smooth, Transparent	**140 ± 0.92**	**0.78 ± 0.02**	**253 ± 2.3**	**26 ± 1.0**
F-4	Thin, Smooth, Transparent	165 ± 1.02	0.92 ± 0.02	243 ± 1.3	28 ± 1.4
F-5	Thin, Smooth, Transparent	176 ± 0.98	1.06 ± 0.04	203 ± 2.2	29 ± 2.2
F-6	Thin, Smooth, Transparent	193 ± 1.62	1.18 ± 0.02	178 ± 3.1	33 ± 3.0

*Each reading is a mean of 3 consecutive reading (±SD)

Surface pH of films: Surface pH was measured to determined formulation having range of salivary pH. Acidic or alkaline pH may produce irritation to oral mucosa. Surface pH for all formulation F-1 to F-6 was found in the range of **6.5 to 6.8.** Surface pH of all films was within the range of salivary pH. No significant difference was found in surface pH of different films.

Drug content of films: Drug content uniformity for all formulation is shown in Table below. Drug content for all formulation was found to be in the range of 91 % to 98.4% which shows uniformity of drug content in all formulation.

Determination of moisture content: The prepared films were weighed and kept in a vacuum desiccator containing anhydrous silica at room temperature. The patches were weighed repeatedly until they showed a constant weight.

Determination of moisture up take: The prepared films were weighed and kept in a desiccators containing anhydrous silica at room temperature for 24 hours. It was then taken out from the desiccator, weighed and exposed to relative humidity of 75% (saturated solution of sodium chloride) in desiccators. The film was weighed until it showed a constant weight.

Table No. 10: Evaluation of Orodispersible films of Fluoxetine HCl

Formulation Code	Tensile Strength (gm/mm^2)	% Elongation	Surface pH	% Drug Content	% Moisture Content	% Moisture Up take
F-1	4.67 ± 0.014	14.21 ± 0.21	6.6	91.15	3.21	1.33
F-2	5.10 ± 0.026	17.83 ± 0.15	6.5	96.53	3.24	1.31
F-3	5.40 ± 0.034	21.23 ± 0.61	6.6	98.40	3.83	1.29
F-4	5.28 ± 0.041	22.39 ± 0.13	6.7	91.10	2.98	1.12
F-5	4.86 ± 0.084	26.81 ± 0.42	6.8	95.90	2.64	1.28
F-6	4.40 ± 0.064	25.00 ± 0.41	6.5	94.02	2.87	1.45

Scanning Electron Microscopy: The determination of surface morphology was done by scanning electron microscope ZEISS-5400, Japan. The scanning electron photomicrograph of the film carried out 10,000 X magnifications. It shows smooth surface of the film.

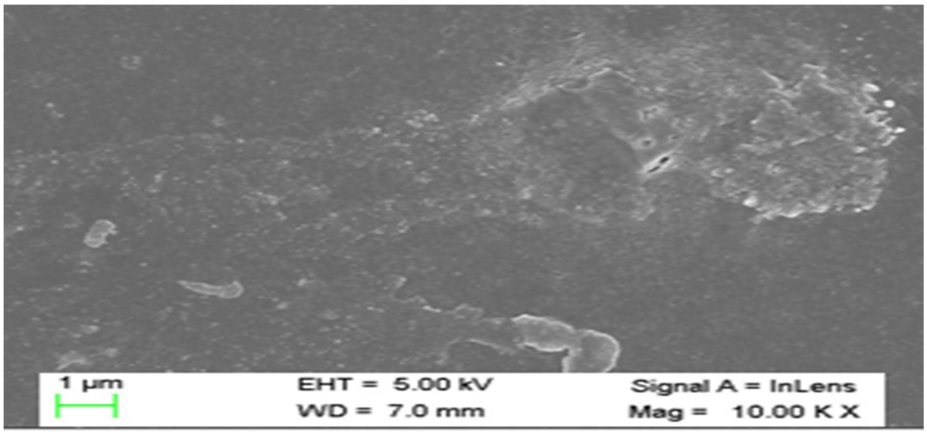

Figure 7: Surface Morphology of the X5 formulation at 10000X

***In-vitro* Dissolution Study:** The *in vitro* drug release study of fast dissolving film from each batch F-1 to F-6 was carried out in phosphate buffer of pH 6.8 solution for 30 min.

Table No. 11: *In-vitro* Drug Release from Orodispersible films of Fluoxetine HCl

Time (min)	Cumulative % of drug release					
	F-1	F-2	F-3	F-4	F-5	F-6
0	16.23	17.32	15.72	16.45	17.77	16.53
2	39.45	40.75	39.96	38.64	39.54	38.65
5	53.23	54.83	55.98	62.32	53.83	52.66
10	56.42	58.43	59.33	68.83	55.38	59.85
15	61.64	62.08	69.76	72.11	58.66	62.06
20	65.55	65.92	74.72	76.26	63.43	67.05
25	68.23	71.38	85.38	78.43	68.76	71.92
30	72.34	78.43	93.37	79.62	74.47	77.34

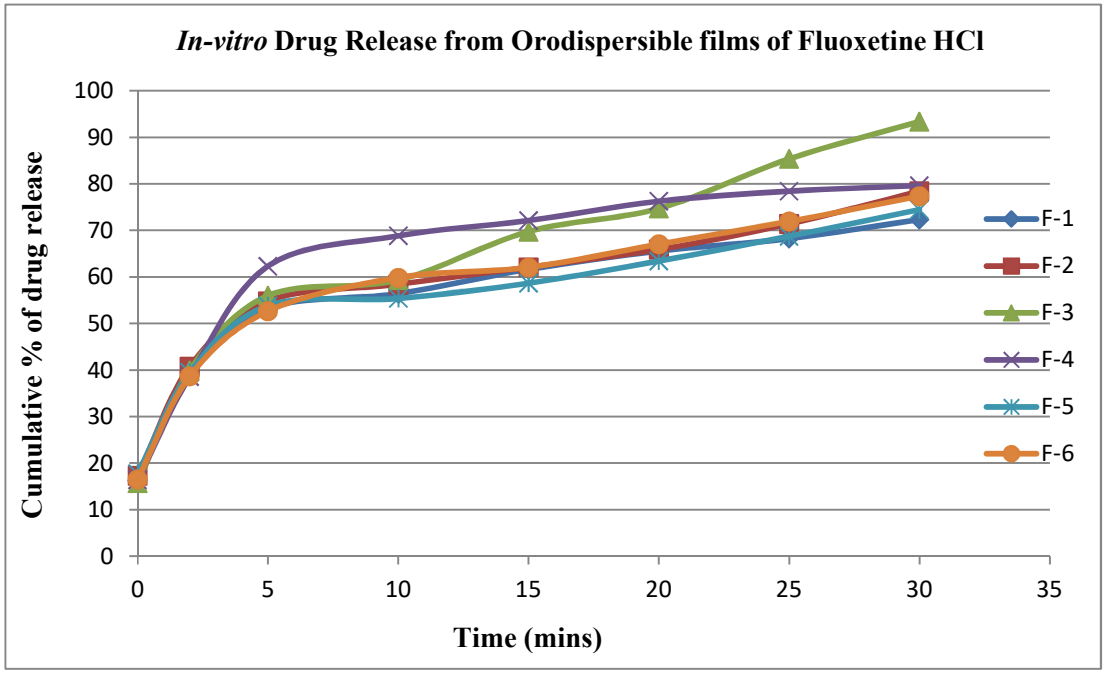

Figure 8: *In-vitro* Drug Release from Orodispersible films of Fluoxetine HCl

From the above results it was observe that as the concentration of polymer increases drug release from film decreases. About 72 to 93.37% drug was released within 30 minute and in all formulation 50 to 60 % drug was released within 5 minute.

On the basis of above drug release studies it was clear that the formulation F-3 was the best among all prepared batches because of highest drug release percentage.

7.3 Kinetics Modeling of Drug Release

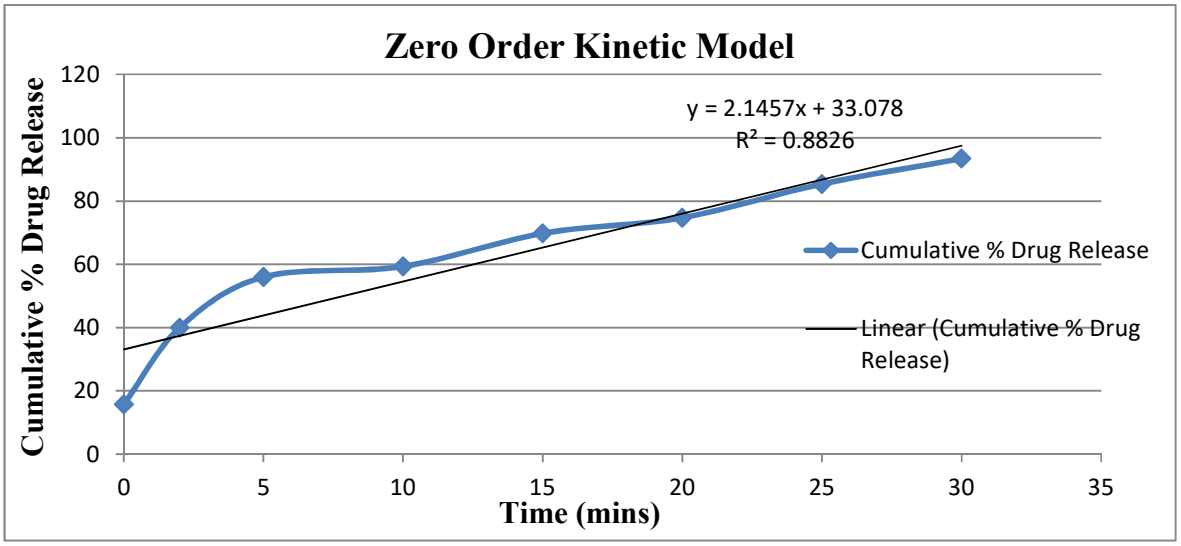

Figure 9: Zero Order Kinetic Model for drug release from F-3

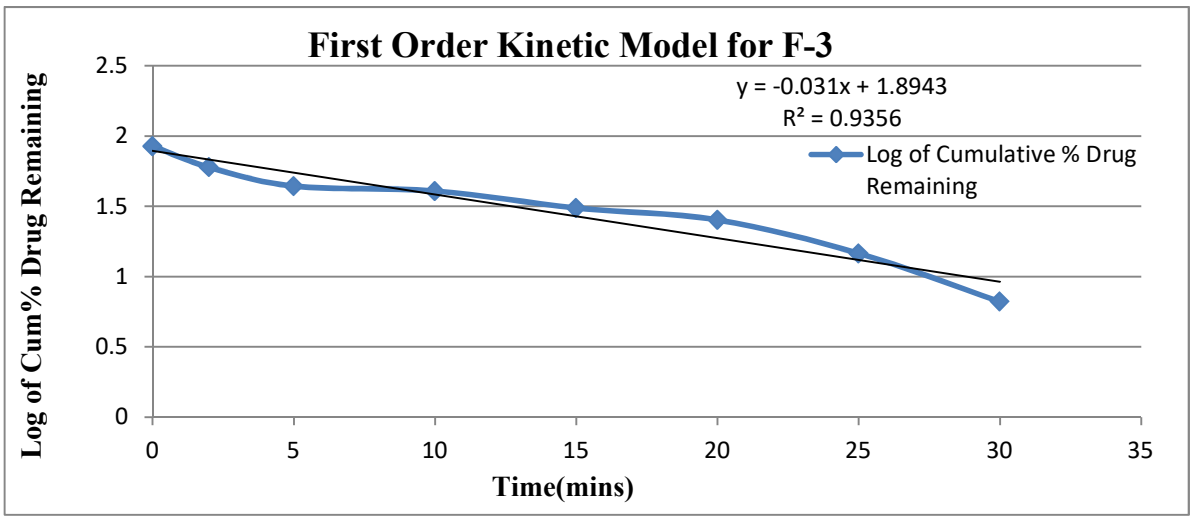

Figure 10: First Order Kinetic Model for drug release from F-3

7.4 Accelerated Stability Study

The accelerated stability studies of optimized formulation (F-3) revealed that there is no significant reduction in drug content, Disintegration time, appearance was observed over period of 3months.

Stability study at room temp 25°C ± 2°C / 75 % RH ± 5% RH and was carried out for 0^{th} and 90^{th} day. At room temperature for 0^{th} and 90^{th} day's drug content was found 98.40 and 96.61and disintegration time was 26 Sec while the % cumulative drug release was found in the range of 93.37 - 92.90%. As the days passes it was seen that there is a reduction in % drug content and also there was a decreased rate in the % cumulative drug release. At 40°C ± 2°C / 75 % RH ± 5% RH 0^{th} and 90^{th} day, drug content was found to be 98.30 to 98.85 and disintegration time was about 26 to 25 while the % cumulative drug release was found in the range of 93.37 to 92.90%. As the days passes it was seen that there is a reduction in % drug content and also there was a decreased rate in the % cumulative drug release. No significant change was observed in drug content and disintegration time at room temperature and as well as on accelerated stability studies at 40°C ± 2°C / 75 % RH ± 5% RH. Hence formulation F-3 was found to be stable for 90days.

CONCLUSION

The present study has been an attempt to formulate oral dispersible film of Fluoxetine HCl with a view of improving its oral disintegration and giving a rapid release of the drug. From the experimental results it can be concluded that, the various polymers were used for screening amongst them the films prepared by HPMC shows good disintegration time. F-3 formulation showed best possible result and was selected as optimized batch. Formulated film gives satisfactory result for various evaluation parameters of films like physical appearance, and surface texture, weight uniformity, thickness uniformity, Folding endurance, Surface pH, Drug content uniformity, In vitro Disintegration time, *In-vitro* drug release. Formulation showed fairly acceptable values for all the evaluation tests. From evaluation it was concluded that disintegration time of the film increased with increased in polymer concentration.

Hence, finally it was concluded that the prepared film of Fluoxetine HCl was a satisfactory attempt to formulate oral dispersible film and may also prove to be a potential candidate for safe and effective oral dispersible drug delivery.

CONFLICTS OF INTERESTS

There are no conflicts of interests.

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