FORMULATION AND EVALUATION OF FAST DISSOLVING THIN STRIPS OF VENLAFAXINE HYDROCHLORIDE

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ABSTRACT

In the current research, Fast dissolving thin strips (FDTS) of Venlafaxine hydrochloride was formulated for the treatment of depression. Depression is considered as a common mental disorder which is generally recognized by depressed mood, low energy level, disturbance in sleep and appetite, weak concentration level, feelings of guilt etc.. The objective is to formulate FDTS of Venlafaxine to overcome the problem of dysphagia and decreased bioavailability bypassing hepatic metabolism. FDTS dissolve or disintegrate in mouth when they came in contact with saliva, as the oral mucosa is highly vascularised so drug directly enter into systemic circulation and provide quick onset of action and instant bioavailability. The FDTS of Venlafaxine were prepared by solvent casting method by using hydrophilic polymers HPMC K4M and Poly Vinyl alcohol , superdisintegrant like crosspovidone, cross carmellose sodium and sodium starch glycolate, plasticizer PEG-400, sweetening agent, saliva stimulating agent etc. The prepared FDTS were evaluated for Surface texture, Appearance, transparency, Weight variation and its value was found within range, Film thickness (0.169 ±0.0077 to 0.192 ±0.0025), Tensile strength (1.62±0.51 to 1.69±0.23), Percent elongation (24±0.89 to 30±0.36), Folding endurance (256±6.11 to 276±8.02), Surface pH (6.35±0.126 to 6.56±0.132), % Moisture uptake (1.82±0.339 to 2.23±0.458), % Moisture loss (1.41±0.462 to 2.39±0.237) % Drug content (94.75 ±0.010 to 97.74±0.031), Disintegration test(12±0.143sec. to 16±0.743sec.), In-vitro dissolution test (92.56 to 97.32). It was evaluated that different superdisintegrant has significant effect on disintegration time, dissolution rate and permeation rate of FDTS of Venlafaxine. From above experimental study it was concluded that FDTS were successfully prepared and evaluated. Prepared formulation are capable to deliver venlafaxine at a rate and extent that may improve its therapeutic effectiveness hence improve patient compliance.

Keywords: - Venlafaxine HCl, Fast dissolving thin strips (FDTS), Dysphagia, Bioavailability, Solvent casting technique.

INTRODUCTION:

The first choice for the administration of therapeutic agent of most patient including all age group is the oral route when compared to the other route of drug administration. It was observed that oral route has various advantages like administration of drug is easy, painless, therapy cost is low and almost drug can be incorporated so the oral route is mostly preferred and accepted route by the patient (Patil et al 2014). After having certain advantages there is still a need of advancements in the oral drug delivery system because of few drawbacks which are observed in the patients having problem of dysphagia (specially paediatric and geriatric) and unresponsive patients because it was seen that that they feel trouble in swallowing and chewing the conventional solid dosage forms like tablets and capsules. As per the estimation it was observed that about 18-22% of patients which are in long term care facilities and 30-40% of elderly patients suffer from dysphagia. Other people which feel laboriousness in swallowing and chewing conventional solid dosage forms include people which are engaged in travelling due to their work and are not able to carry water each and everywhere and suffering from any medical conditions (Bera et al. 2013). An estimation was done which indicates that about 50% of overall community faced the problem of dysphagia which ultimately results in inadequate therapy and leads to patient incompliance. Various research and experiments have been done by each and every industry in the field of oral drug delivery system to overcome the associated problems which mainly include transformation of the dosage form from available simple conventional tablets or capsules to modified release tablets or capsules. In this order, in late 1970's Fast dissolving drug delivery system came into light which include fast dissolving tablets and fast dissolving films (Patel et al. 2010).

Fast dissolving drug delivery system which is another type of oral drug delivery system generally based on the technology used in case of transdermal patch. This system include such dosage forms which quickly disintegrates or dissolves in the oral cavity when came in contact with saliva which provides faster and better absorption through buccal mucosa and reach directly into the systemic circulation which results in quick action and increased bioavailability. (Patil et al 2014)

Venlafaxine hydrochloride is an antidepressant which belongs to a category of drugs called selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). (Venlafaxine Hydrochloride Monograph for Professionals - Drugs.com [Internet]. Drugs.com. 2018). Depression is considered as a common mental disorder which is generally recognized by depressed mood, low energy level, disturbance in sleep and appetite, weak concentration level, feelings of guilt etc. (WHO.int. 2018) When these condition affect for short period of time than it is not considered as harmful but when it last for long period of time approximately two weeks or more

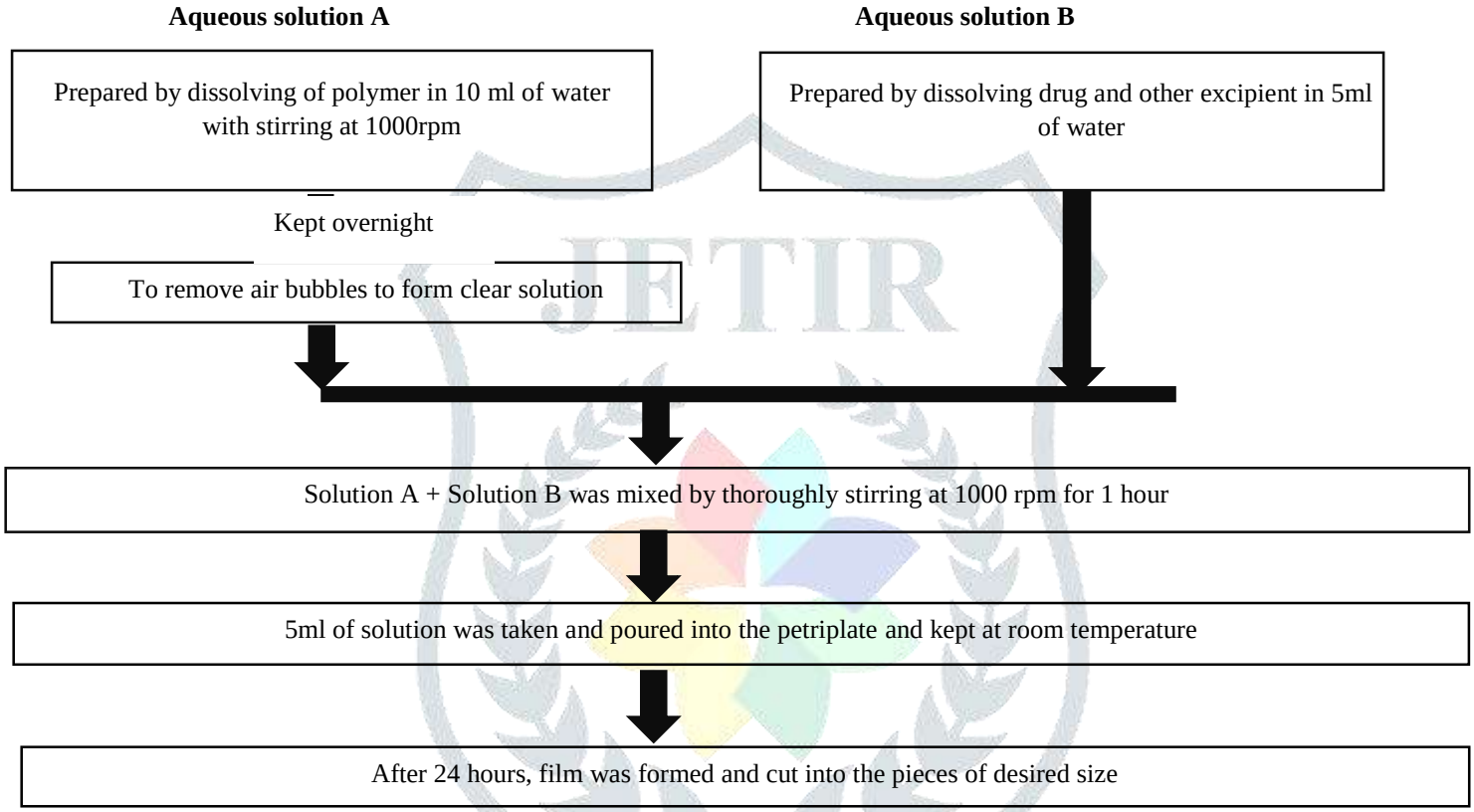
and effect day to day habits or activities than it is considered as depressive disorder. Venlafaxine hydrochloride act by affecting chemicals in the brain that may be disturbed in people suffering from the problem of depression. Venlafaxine hydrochloride is used for the treatment of generalized and social anxiety disorder, major depressive disorder and panic disorder. Its reduced bioavailability makes it a suitable candidate for oral fast dissolving drug delivery system. (Drugbank.ca. 2018)

MATERIALS AND METHODS:

Venlafaxine hydrochloride was obtained as a gift sample from the Ranbaxy laboratories. HPMC K4M was procured from Balaji drugs. PVA and poly ethylene glycol 400 was procured from Central Drug House, New Delhi. Other ingredients which were used are of pharmaceutical grade.

Formulation of Fast dissolving thin strips of Venlafaxine Hydrochloride

Fast dissolving thin strips was prepared by using Solvent casting technique.



Composition of fast dissolving thin strip

Composition of different Venlafaxine hydrochloride fast dissolving thin strips by using solvent casting technique was shown in Table 1.

Evaluation of fast dissolving thin strips

Organoleptic Evaluation:

- **Appearance: -** Appearance of the formulated strips was done by visual inspection and then strips were categorised as best, good, average and bad.
- **Transparency: -** Transparency evaluation of formulated strips was done by visual inspection and then strips are categorised as transparent, semi-transparent and opaque.
- **Surface texture:** - Surface texture of formulated strips was done by visual method by visual inspection and strips were categorised from smooth to rough surface which indicated by ++ mathematical signs. (S. Raju et al.2011)

Weight Uniformity:

For calculation of weight uniformity 3 films from each formulation were taken and weighed individually by using digital balance. The weight of each film was noted down. Then average weight and standard deviation was calculated. (Agarwal et al. 2011)

Thickness:

The thickness of the formulated films was calculated with the help of the vernier calipers. The thickness of the film was measured at different places and the average thickness was calculated and standard deviation was calculated. (Ali et al.2016)

Tensile strength: -

For determination of tensile strength digital tensile tester was used. The film of specific was used for this test. The films was pulled by upper clamp at suitable speed and lower clamp was in stationary phase. Tensile strength is defined as the maximum stress applied up to the point at which the strip starts breaking. It is calculated by dividing applied load at breakage with a cross-sectional area of the strip. (Shinkar et al. 2017)

$$\text{Tensile strength} = \frac{\text{Load of breakage}}{\text{Strip thickness X Strip width}}$$

Percent Elongation: -

When stress or tension is applied, a sample of film stretches and this referred as strain. The increased length of the film was noted down and this experiment was performed in triplicate. Mean and standard deviation was calculated. (Shinkar et al. 2017)

$$\% \text{ Elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100$$

Folding endurance:-

Folding endurance of formulated strips was determined by repeatedly folding the films (3 films from each formulations) of $2cm^2$ at the same place till the films breaks or crack has been observed. The number of folds (number of times at which the strips was folded at the same location) without breaking was noted down and standard deviation was calculated. (Juluru 2013)

Surface pH: -

For the determination of surface pH digital pH meter was used. The films of $2cm^2$ was cut and dissolved in 5 ml of distilled water. The pH of the film was measured by keeping the electrode in contact with the solution for 1 minute by allowing it to equilibrate. The experiment is repeated by using 3 strips from each formulation average value is calculated and standard deviation were reported. (Agarwal et al. 2011)

Percent Moisture uptake: -

This test is usually done to determine the physical stability of the strips in high humid conditions. . For the determination of % moisture loss 3 films of $1cm^2$ was taken and weighed individually by using digital balance. Now, the film were placed in desiccator for the period of 72 hours. After 72 hours the strips were removed and exposed to the saturated solution of aluminium chloride and reweighed. The average percent moisture loss of film was calculated by using formula:- (Vijaya sri et al.2013)

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial Weight}}{\text{Final weight}} \times 100$$

Percent Moisture loss:

This test is usually done to determine the physical stability and integrity of the formulated strips at dry conditions. For the determination of % moisture loss 3 films of $1cm^2$ was taken and weighed individually by using digital balance. Now, the film were placed in desiccator containing fused anhydrous calcium chloride (inside the desiccator) for the period of 72 hours. After 72 hours the strips were removed and reweighed. The average percent moisture loss of film was calculated by using formula:- (Vijaya sri et al.2013)

$$\% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial weight}} \times 100$$

Drug content uniformity:

The film of $1cm^2$ was taken and dissolved in 25ml of phosphate buffer pH 6.8. Then the solution was sonicated for 15minutes with the help of sonicator for complete solubilisation of film. Then the solution was filtered through Whatman filter paper. If necessary dilution was done and the solution was analysed by using UV- spectrophotometer at 275nm for the determination of absorbance. This experiment is repeated by using 3 films from each formulation and absorbance was noted down to obtain the average value and further calculation was done to determine the percent drug content. (Londhe et al. 2012)

***In – vitro* disintegration test:**

In-vitro disintegration test was done by using petridish method. In this method 2-3ml of distilled water was taken in the petridish and the film of $1cm^2$ was placed on the petridish. The time required by the film to dissolve was noted down. This experiment is done by using three strips from each formulation. After that average was calculated and standard deviation was calculated. (Lakshman et al. 2017)

***In – vitro* dissolution studies:**

In-vitro dissolution studies was performed by using USP (Type II) dissolution apparatus. For this phosphate buffer 6.8 was used as a dissolution medium and the temperature was maintained at 37±0.5˚C. A film of 1cm^2 was placed into the dissolution apparatus and the medium was stirred at speed of 50rpm. From the solution aliquots (5ml) of sample was taken at 1minute time interval and same volume was maintained by replacing with freshly prepared same dissolution medium. The absorbance of the samples was measured at 275nm respectively by using UV-Visible spectrophotometer against an appropriate blank. (Sharma et al. 2015)

***In- Vitro* Kinetic study:-**

For the release kinetic study the data obtained from the *in-vitro* dissolution studies was incorporated to zero order, first order, higuchi matrix and korsmeyer peppas model. The aim behind the kinetic study was to determine the release mechanism of drug from the dosage form. This was done by comparing the r^2 value of each formulation which determine the best fit model and by observing the n value of all the formulation which gives the idea of mechanism of drug release from the prepared formulation.

- **Zero Order: -** The graph was plotted between % Cumulative release v/s time.
- **First order: -** The graph was plotted between Log % ARA v/s time.
- **Higuchi matrix: -** The graph was plotted between % Cumulative release v/s √T.
- **Korsmeyer- peppas model: -** The graph was plotted between Log % Cumulative release v/s Log t. (Chauhan et al. 2012)

***In-vitro* permeation studies:-**

In- vitro permeation studies was carried out by using Franz diffusion cell. For this, egg shell membrane was used to resemble the buccal mucosa and phosphate buffer 6.8 was used as a medium. The membrane was placed between the donor and the receptor compartment. The receptor compartment was filled with the suitable volume of the medium and the temperature was maintained at 37˚C and then it was placed over the magnetic stirrer for maintain the hydrodynamics. Then the film of 1cm^2 (25mg drug) was placed on the donor compartment. Then from the receptor compartment aliquots (2ml) of sample was taken at 1minute time interval and same volume was maintained by replacing with freshly prepared same dissolution medium. The absorbance of the samples was measured at 275nm respectively by using UV-Visible spectrophotometer against an appropriate blank. (Jagannathan et al. 2015)

RESULT AND DISCUSSION:

As per the visual and physical inspection it was observed that all the prepared formulation shows good transparency smoothness and surface texture shown in Table 2.

The weight of all prepared formulation was observed in between 0.0385±0.515 to 0.0420±0.486. As per the obtained result all strips are relatively similar in weight which shows uniform distribution of API and excipient on the surface of the strips shown in Table 3.

The thickness of all prepared formulation was found in between 0.169 ±0.0077 to 0.192 ±0.0025. As per the obtained result it was observed there is no remarkable change in the thickness of the strips so it can be concluded that there is uniform distribution of API and excipient throughout the surface of the films shown in Table 3.

The tensile strength of all formulation ranging between 1.62±0.51 to 1.69±0.23. It generally determines the flexibility of the film to withstand rupture. The Formulation F2 shows the maximum strength 1.20±0.2. It may be due to formation of strong hydrogen bonds between polymer and plasticizer therefore imparting flexibility to withstand rupture shown in Table 3.

The value of percent elongation generally determines the flexibility and its value ranging between 24±0.89 to 30±0.36 shown in Table 3.

The value of folding endurance of all prepared formulations was found in between 256±6.11 to 276±8.02.As per the obtained result it was observed all strips are relatively similar in folding endurance. The folding endurance value generally determines the ability of the strips to withstand rupture shown in Table 3.

The value of pH of all prepared formulations was observed in between 6.35±0.126 to 6.56±0.132. As per the obtained value it was observed that the pH value of all the strips is near to neutral (there is no remarkable difference in pH of the film and pH of saliva) which indicate that there will be not any kind of irritation or side effects to the mucosal lining of the oral cavity after administration of the formulated films shown in Table 4.

The value of percent moisture uptake of all prepared formulation observed in between 1.82±0.339 to 2.23±0.458 (Table No.7.14). The percentage moisture uptake value generally determines the physical stability of the formulated strips when exposed to high humid conditions shown in Table 4.

The value of percent moisture loss of all prepared formulation ranges was found in between 1.41±0.462 to 2.39±0.237 (Table No. 7.15). The percentage moisture loss value generally determines the physical stability and integrity of the formulated strips when exposed to dry conditions shown in Table 4.

The value of drug content of all prepared formulations was found in between 94.75 ±0.010 to 97.74±0.031 (Table No. 7.16). As per the obtained value it was observed that there is very less difference in the drug content value of all formulations which indicate good uniformity of drug all over the surface of the strips shown in Table 4.

The value of *in-vitro* disintegration study of formulated films ranges from 12±0.143 to 16±0.743. As per the obtained value it was observed that there no significant difference in disintegration time of all formulation but the formulation F2 which contain HPMC K4M as hydrophilic polymer and crosspovidone as superdisintegrant shows less disintegration time as compared to other formulation shown in Table 4.

The cumulative percent drug release from all prepared formulation was ranging from 92.56 to 97.32 shown in Table 5 and Figure 1 during study period. From the in-vitro dissolution studies it was observed that the formulation F2 containing HPMC K4M as film forming polymer and crosspovidone as superdisintegrant shows maximum drug release (97.32%) within 5 minutes. The rate of drug release was faster because the solubility of HPMC K4M was high and the crosspovidone which was used as superdisintegrant act by combination of three mechanism wicking, swelling and deformation which ultimately leads to the higher wettability and penetration of water in the film matrices which increased the rate of dissolution of drug.

From the obtained experimental graph for kinetic study shown in Figure 2, Figure 3, Figure 4 Figure 5 and it was clearly observed that by comparing the r^2 value zero order is most dominant in F2, F3, F4, F5, F6 formulation except F1 which means that the drug release is dependent on the time shown in Table 6. By observing the value of release exponent (n) from korsmeyer peppas model it was concluded that the non-fickian or anamolus diffusion was dominant in which the release of the drug the film matrices was depend on the polymeric chains relaxation when came in contact with the solvent.

The % drug permeation of all the prepared formulation was ranging from 85.21% to 93.25% shown in Table 7 and Figure 6 during study period. The formulation F2 which contain HPMC K4M as film forming polymer and crosspovidone as superdisintegrant shows maximum drug permeation (93.25%) within minimum time (11minutes) period when compared to other formulation which indicates excellent drug permeation, which is the basic requirement in case of fast dissolving formulation to minimise the first pass metabolism of drug to enhance the bioavailability and for faster onset of action.

CONCLUSION:

The present research works indicates that fast dissolving thin strips of venlafaxine hydrochloride was considered as a good alternative in case of depression where immediate action is required. It was observed that at present time 30-40% elderly people were suffering from problem of depression and they also feel difficulty in swallowing tablets and capsules. As the drug having low bioavailability due to first pass metabolism FDTS of drug was considered because it leads to quick disintegration and dissolution hence quick onset of action. Finally, from the research work it was concluded that by use of crosspovidone as superdisintegrant the drug release from the strips was faster as compared to other formulations which was the basic requirement for people suffering from the problem hence increased bioavailabilty and improved patient compliance.

CONFLICT OF INTEREST:

The authors have no conflict of interest.

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Table 1: Composition table of fast dissolving thin strips of Venlafaxine hydrochloride

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Venlafaxine HCl (mg)	25	25	25	25	25	25
HPMC K4M (%)	3%	3%	3%	-	-	-
Poly Vinyl Alcohol (%)	-	-	-	3%	3%	3%
Polyethylene glycol (ml)	5	5	5	5	5	5
Cross povidone (mg)	-	30	-	-	30	-
Cross carmellose sodium (mg)	30	-	-	30	-	-
Sodium starch glycolate (mg)	-	-	30	-	-	30
Citric acid (mg)	10	10	10	10	10	10
Mannitol (mg)	25	25	25	25	25	25
Aspartame (mg)	5	5	5	5	5	5
Water(ml)	10	10	10	10	10	10

Note: - 1cm^2 contain 25mg of the drug Venlafaxine hydrochloride.

Table 2: Organoleptic properties

Formulation code	**Appearance**	**Transparency**	**Surface texture**
F1	Good	Transparent	+++
F2	Best	Transparent	+++
F3	Good	Transparent	+++
F4	Good	Transparent	+++

F5	Average	Transparent	++-
F6	Good	Transparent	+++

Table 3: Evaluation result of formulated films

Formulation Code	Weight (gm) Mean ± S.D. (n=3)	Thickness (mm) Mean ± S.D. (n=3)	Tensile Strength Mean ± S.D. (n=3)	Percent elongation Mean ± S.D. (n=3)	Folding endurance Mean ± S.D. (n=3)
F1	0.0385±0.51	0.169±0.0077	1.67±0.59	29±0.14	256±6.11
F2	0.0409±0.31	0.175±0.0043	1.69±0.23	30±0.36	267±4.58
F3	0.0401±0.47	0.173±0.0097	1.68±0.19	26±0.74	264±7.63
F4	0.0420±0.52	0.190±0.0025	1.64±0.21	25±0.51	272±11.1
F5	0.0419±0.84	0.186±0.0062	1.65±0.14	27±0.54	262±6.02
F6	0.0420±0.48	0.192±0.0025	1.62±0.51	24±0.89	276±8.02

Table 4: Evaluation result of formulated films

Formulation code	Surface pH Mean ± S.D. (n=3)	Percent moisture uptake Mean ± S.D. (n=3)	Percent moisture loss Mean± S.D. (n=3)	% Drug content Mean ± S.D. (n=3)	Disintegration Time (seconds) Mean ± S.D. (n=3)
F1	6.44±0.07	1.86 ±0.23	2.10±0.18	94.75 ±0.010	14±0.51
F2	6.56±0.13	1.82±0.33	1.41±0.46	97.74±0.031	12±0.14
F3	6.40±0.14	2.05±0.18	1.52±.0.18	95.12±0.052	13±0.54
F4	6.44±0.05	2.19±0.16	2.30±0.26	94.57±0.080	15±0.41
F5	6.51±0.15	2.12±0.14	2.21±0.17	96.08±0.042	13±0.62
F6	6.35±0.12	2.23±0.45	2.39±0.23	94.98±0.035	16±0.74

Table 5: Cumulative % drug release data of prepared formulations

S.No.	Time (min)	% Cumulative Release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	23.15	26.5	24.95	21.05	22.25	21.56
3	2	46.9	52.9	49.56	39.07	42.98	41.25
4	3	63.21	69.5	65.42	55.28	58.41	56.23
5	4	76.56	84.94	81.64	69.56	73.21	71.21
6	5	89.23	97.32	94.02	83.01	86.73	84.21
7	6	95.52	-	-	92.56	95.21	93.89

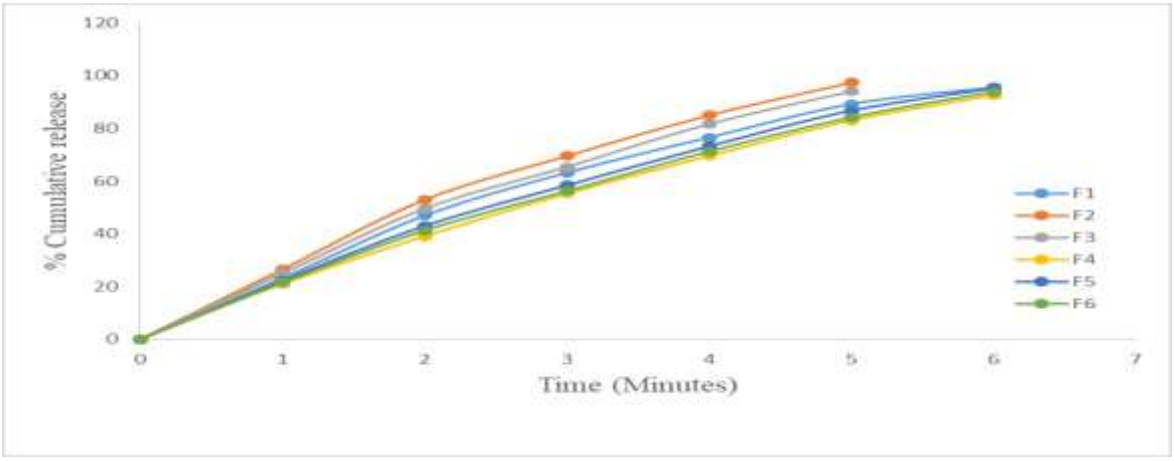

Figure 1: *In-vitro* drug release data of prepared formulation F1 to F6

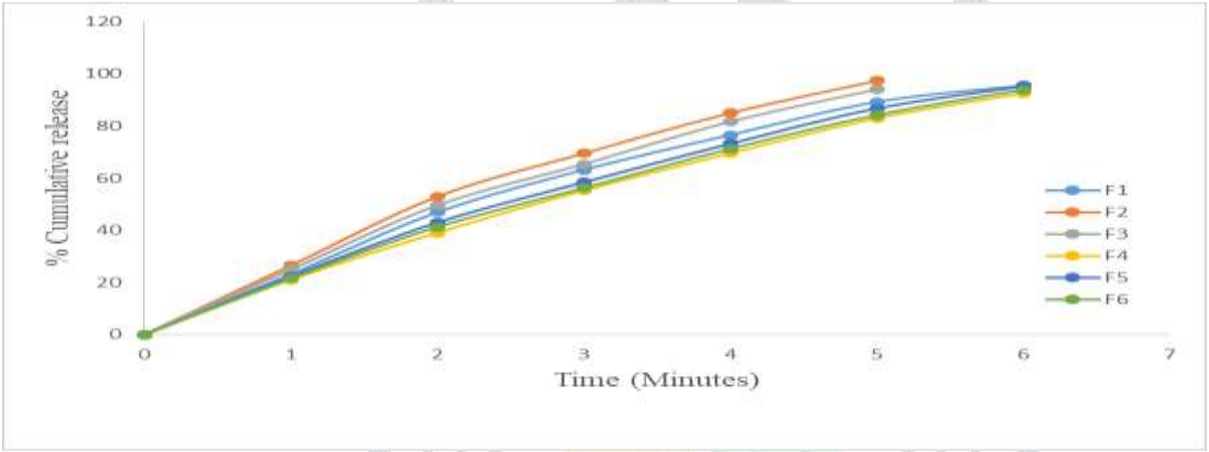

Figure 2: Zero-order kinetic profile of formulations F1 to F6

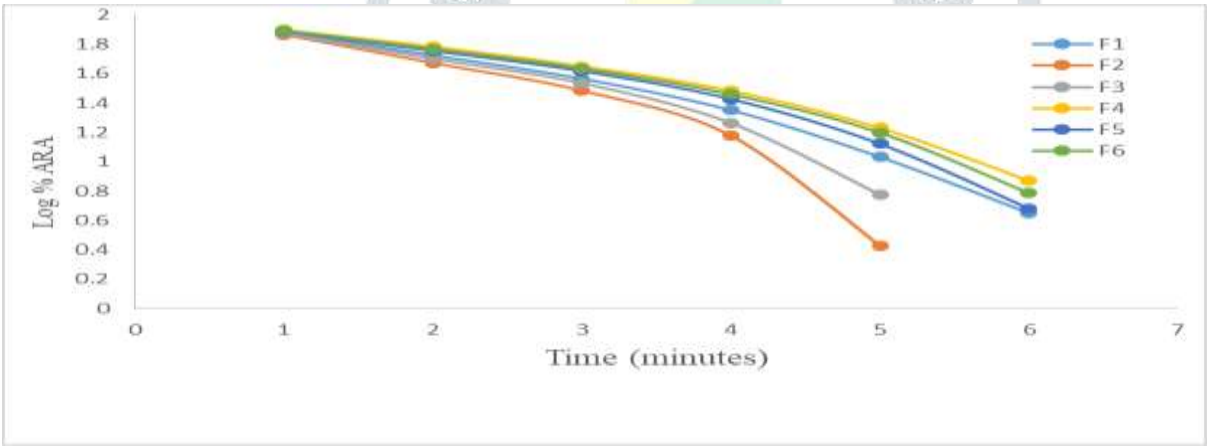

Figure 3: First-order kinetic profile of formulations F1 to F6

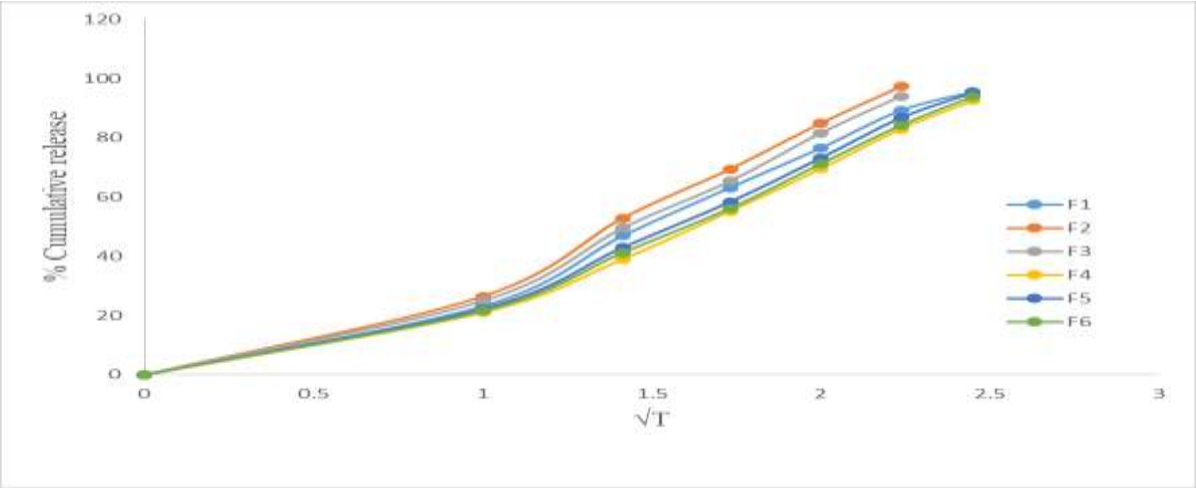

Figure 4: Higuchi matrix kinetic profile of formulations F1 to F6

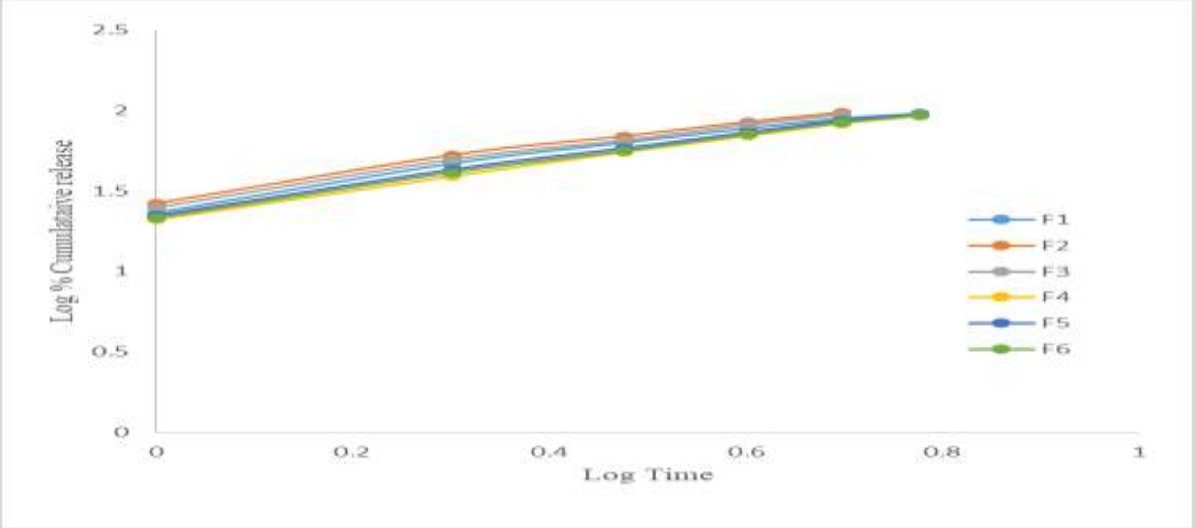

Figure 5: Korsmeyer – peppas kinetic profile of formulations F1 to F6

Table 6: Result of Correlation coefficients data of prepared formulations F1 – F6

S. No.	Formulation code	r^2			n	Best fit model	Mechanism of Release
		Zero order	First order	Higuchi matrix			
1	F1	0.9654	0.9645	0.9686	0.795	Higuchi	Non-fickian
2	F2	0.9874	0.8984	0.9665	0.806	Zero order	Non- fickian
3	F3	0.9815	0.9414	0.9716	0 .822	Zero order	Non-fickian
4	F4	0.9819	0.9498	0.9584	0.901	Zero order	Non-fickian
5	F5	0.9759	0.9387	0.9647	0.815	Zero order	Non-fickian
6	F6	0.9849	0.9415	0.9619	0.824	Zero order	Non-fickian

Table 7: *In- vitro* permeation study data of prepared formulations

S.No.	Time (min)	% Drug permeate					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	1	11.92	14.26	13.98	10.98	11.08	10.57
3	2	22.53	26.47	24.13	18.56	20.98	17.96
4	3	31.56	36.98	34.58	25.54	28.21	23.92
5	4	39.58	47.56	44.56	32.36	36.75	29.54
6	5	48.98	55.98	51.53	39.51	44.97	37.63
7	6	56.12	63.59	59.56	46.57	51.59	44.95
8	7	62.82	70.28	66.74	53.01	58.54	51.58
9	8	68.01	76.53	73.53	58.72	65.76	57.31
10	9	75.91	83.95	78.98	64.82	71.57	62.23
11	10	79.48	88.23	84.57	71.71	76.21	68.41
12	11	84.43	93.25	87.53	75.18	81.51	73.91
13	12	88.56	-	91.58	79.98	86.64	77.92
14	13	91.45	-	-	83.58	90.56	81.58
15	14	-	-	-	87.61	-	85.21

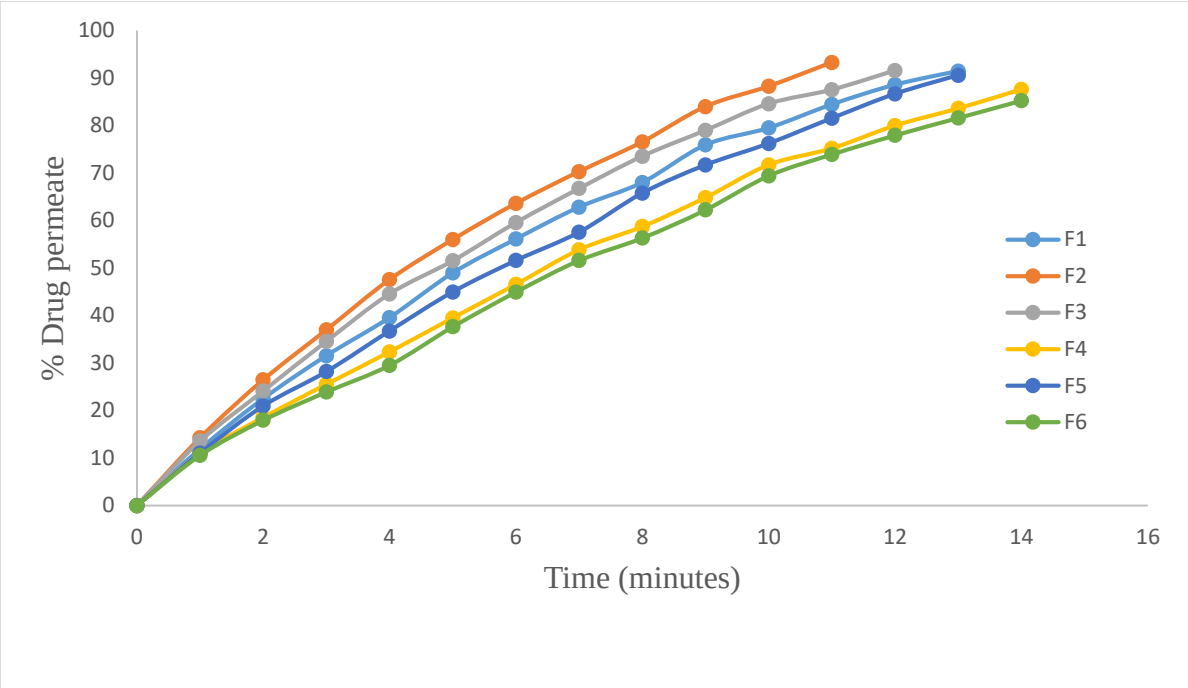

Figure 6: - *In-vitro* permeation of formulations F1 to F6