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Fabrication and *in vitro* evaluation of Venlafaxine Hydrochloride mini tablets filled hard Gelatin Capsules

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Abstract

The main objective of present work is to develop mini tablets filled hard gelatin capsules. Mini tablets filled hard gelatin capsules drug delivery system comprises of 5 matrix mini-tablets weighing 50 mg encapsulated in hard gelatin capsule (size 00). For achieving the sustained release, various viscosity grades of Hydroxy propyl methyl cellulose polymer (HPMC K4M, K100M, K200M) and Kollidone were used. The mini-tablets were prepared by wet granulation method. The prepared mini-tablets were subjected for pre-compressional and post-compressional evaluation. The compatibility of drug with ingredients used were checked by DSC and FTIR studies. Accelerated stability studies were carried out as per ICH guidelines for the best formulation. The pre-compression and post compression parameters were within prescribed limits. The *in vitro* performance of the best formulation showed sustained drug release for a period of 12 h. The DSC and FTIR results revealed that there was no interaction between drug and excipients used. The best formulation retained its physicochemical characteristics even after stressed storage conditions.

Keywords: Mini-tablets, hard gelatin Capsule, Hydroxy propyl methyl cellulose, Kollidone

Introduction

The concept of multi-unit dosage forms were initially introduced in the early 1950s. They show reproducibility of the sustained release profiles when compared single unit dosage forms. In multi-unit dosage forms the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits. The normal size of mini tablets are with a diameter of 3mm. From the production point of view mini tabletting technique has advantages over pellets, as it does not require any solvents for its production, defined size and strengths can easily be produced with good batch to batch uniformity. Mini tablets filled into hard capsules, after disintegration, release these subunits as multiple dosage forms [1]. Venlafaxine Hydrochloride is a unique. Venlafaxine HCl and its active metabolite, o-desmethylvenlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine, but have no monoamine oxidase inhibitory activity and a low affinity for brain muscarinic, cholinergic, histaminergic or alpha adrenergic receptors. Hence, it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. The steady state half-lives of Venlafaxine HCl and ODV are 5 h and 11 h, respectively, necessitating the administration, 2 or 3 times daily so as to maintain adequate plasma levels of drug [2-4].

Material and Methods

Materials

Venlafaxine HCl was obtained from Mylan Pharmaceuticals, Hyderabad. HPMC (K 100M, K 4M, K 200M), Carbopol 71 G and Kollidone, Aerosil, magnesium stearate were purchased from Esteem laboratories Pvt. Ltd., Hyderabad, India. All other chemicals used were of AR grade and double distilled water was used whenever necessary.

Methods

Differential Scanning Calorimetry

The DSC measurements were performed on a DSC-6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyser. All accurately weighed samples were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of $10^{\circ}\text{C min}^{-1}$ from 30°C to 300°C . An empty aluminum pan was used as reference.

Fourier Transform Infrared Spectroscopy

FTIR spectra were obtained by using an FTIR spectrometer-430 (Bruker FTIR - Fourier Transform Infrared Spectrometer Model TENSOR 27). Venlafaxine HCl was thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1} , from 4,000 to 300 cm^{-1} . The compatibility of Venlafaxine HCl with HPMC K 100M and Carbopol 71 G was examined.

Method

Preparation of the biphasic delivery system

The formulation process of mini-tablet-in-capsule system can be divided into 2 steps viz., formulation/production of mini tablets and Filling of these mini-tablets in hard gelatin capsules [5-11].

Prolonged-release component (mini-tablets)

The mini-tablets contained either HPMC or kollidone as controlling agents.

Fast release component

Aerosil was used because of its good compaction and disintegration properties. Sodium Croscarmellose was used as a super disintegrant to obtain an immediate release of the drug.

Formulation/production of mini tablets:

Granules were prepared using wet granulation method. All the ingredients in different proportions varying according to the experimental design were passed through 30 mesh. The granules obtained were dried for 1 h in thermostatic hot air oven maintained at $30\text{-}35^{\circ}\text{C}$ to a moisture content of 2-3%.

The lubricated granules were compressed into mini-tablets weighing 50 mg using 6.3 mm round convex punches in a rotary tablet press.

Filling of mini tablets in hard gelatin capsules

The prepared mini tablets were placed in hard gelatin capsule to achieve various extended release profiles of the encapsulated mini-tablet system. The size of the tablets must be controlled so that the tablets can fall freely move into the capsule body.

Table 1. Composition of mini tablets

Ingredients (mg)	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
Venlafaxine	10	10	10	10	10	10	10	10
HPMC K100 M	30	15	-	-	-	-	-	-
HPMC K4 M	-	-	30	15	-	-	-	-
HPMC K200 M	-	-	-	-	30	15	-	-
Kollidone	-	-	-	-	-	-	30	15
Carbopol 71 G	15	15	15	15	15	15	15	15
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation

Compatibility studies

Differential scanning calorimetric (DSC) analysis

The DSC analysis was carried out using Differential Thermal Analyzer (Shimadzu DSC-60, Shimadzu Limited, Japan). Formulation blend (F5) was weighed into aluminum crucible and the DSC thermo grams were recorded at a heating rate of $10^{\circ}\text{C}/\text{min}$ in the range 30°C to 300°C , at a nitrogen flow of 20 ml/m.

Fourier Transform Infrared Spectroscopic (FTIR) analysis

The compatibility of Venlafaxine with excipients used were tested by using Fourier Transform Infrared (FTIR) spectrophotometer (Perkin Elmer, spectrum-100, Japan) using the KBr disk method (5.0122 mg sample in 300.0014 mg KBr). The scanning range was 500 to 4000 cm^{-1} and the resolution was 1 cm^{-1} . This spectral analysis was employed to check the compatibility of drugs with the polymers used.

Pre compressional Parameters

Angle of repose

The angle of repose is determined by fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h , which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation ^[12].

$$\Theta = \tan^{-1}(h/r)$$

Where, Θ is the angle of repose, ' h ' is height of pile, ' r ' is radius of base of the pile.

Bulk density and tapped bulk density

Bulk density and tapped bulk density was determined. A quantity of 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10 ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas [12-13].

LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

Compressibility index:

The compressibility index of the granules was determined by Carr's Compressibility index [12-13].

$$\text{Carr's index (\%)} = [(TBD - LBD) \times 100] / TBD$$

Where, LBD: Weight of the powder/volume of the packing.

TBD: Weight of the powder/Tapped volume of the packing.

Hausner ratio:

Hausner ratio can be determined by the following equation [12-13].

$$\text{Hausner ratio} = TBD / LBD$$

Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

Post Compressional Parameters

Uniformity of Weight

The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually, calculating the average weight and comparing the individual mini-tablet weights to the average [12-13]. The specification of weight variation is 10%.

Hardness

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm². Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated [14].

Thickness

The thickness of ten randomly selected core/coated tablets from each batch was individually recorded in mm using a digital caliper (Mitutoyo digimatic caliper, Mitutoyo Corporation, Japan) and screw gauge. The mean and standard deviation values were calculated from each value recorded.

Friability

A friability test was conducted on the mini-tablets using a veego friabilator. Twenty mini-tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The mini-tablets were initially weighed (W_{initial}) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the mini-tablets were removed. Any loose dust was removed from the mini-tablets as before and the tablets were weighed again (W_{final}). The percentage friability was then calculated by following formula [12].

$$\% \text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

Drug content uniformity

Five mini-tablets weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100 ml of dissolution medium to give a concentration of 100 µg/ml. Take 15 ml of this solution and diluted it up to 100 ml with same solution to give a concentration of 15µg/ml. Absorbance measured at respective wave length using UV-Visible spectrophotometer.

In vitro drug release: Mini-tablets were subjected to *in-vitro* drug release studies in water to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus I at 50 rpm, 37±0.5°C, and water (900 ml) for 2 h, since the average gastric emptying time is about 2 h. The dissolution experiment continued for another 10 h. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis at required wave length [15].

Accelerated Stability studies

A short term accelerated stability studies were performed for the best formulation by storing the tablets at 40°C/75% RH over a 3 months period according to ICH guidelines. At regular intervals for the period of three months, the tablets were examined for any physical characteristics, drug content and *in vitro* drug release.

Results and Discussions

The DSC curve of pure Venlafaxine HCl exhibited a single endothermic response corresponding to the melting of drug. Onset of melting was observed at 215.19°C, the corresponding heat of fusion (ΔHF) was 814.1145 J/g (Fig. 1A), where as in DSC thermo gram of the drug with polymer (formulation blend F2) melting was observed at 215.19°C, the corresponding heat of fusion (ΔHF) was 814.1145 J/g (Fig. 1B).

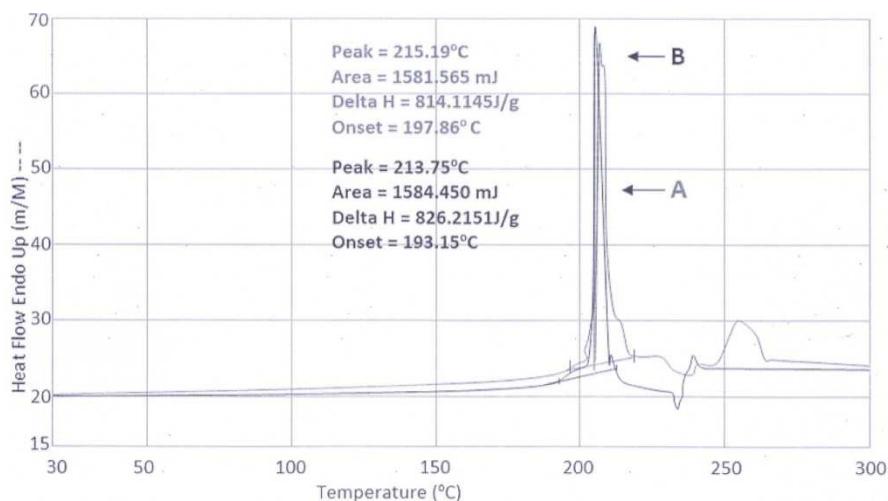


Fig 1. A) DSC endotherm of Venlafaxine HCl pure drug B) DSC endotherm of formulation (F2)

The FTIR spectrums of Venlafaxine HCl with polymers used (HPMC K100 M, HPMC K4 M, HPMC K200M, Kollidone, Carbopol 71G and other excipients) were compared with the standard spectrum of Venlafaxine HCl (Fig. 2). The characteristic bands found in FTIR spectrum of Venlafaxine HCl were found in FTIR spectrum of the blend, indicating that no physical interaction between the drug and polymers used.

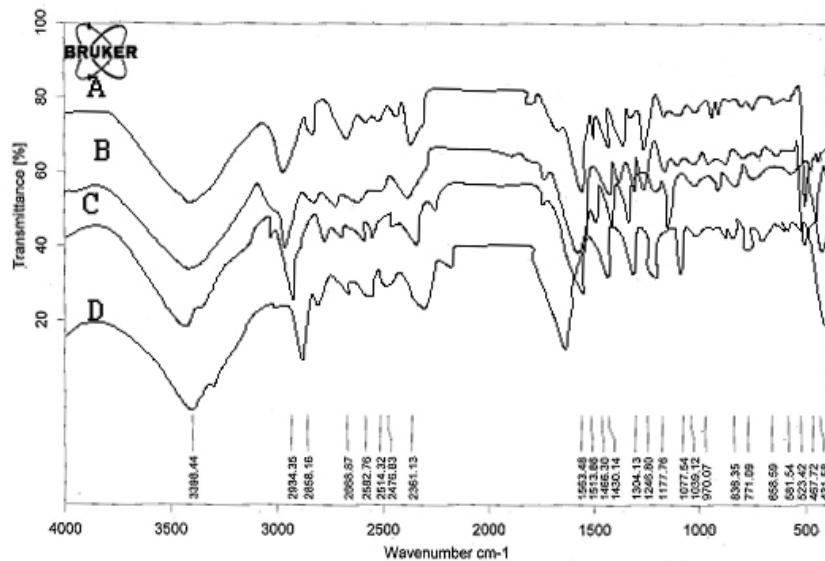


Fig.2. FTIR spectrums of A) Venlafaxine pure drug B) Drug+ HPMC K100 M+ HPMC K4 M+ HPMC K200M C) Drug+ Kollidone D) Formulation blend (F2)

The result of angles of repose for the blend of all formulations indicates the excellent flow properties. The values of loose bulk density and tapped bulk densities were required to calculate Compressibility Index and Hausner's ratio. The Carr's Index and Hausner's ratio indicates the good flow ability of the powder formulation. The results of the flow properties were shown in Table 2.

The variation in weight and thickness of prepared tablets were within the range and complying with pharmacopoeial specifications. The hardness for different formulations was found to be more than 4 kg/cm² and passes the hardness test. The loss on friability was found to be less than 1%, indicates the formulated tablets have good mechanical strength. The drug content in all the formulations was found to be uniform. All these values were represented in Table 3.

Table 2: Results of Pre-compressional parameters of mini-tablets

Formulation	Angle of Repose	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio
F1	24.68±0.031	0.52±0.04	0.62±0.061	16.12±0.75	1.19±0.020
F2	25.16±0.090	0.58±0.048	0.69±0.214	15.94±0.42	1.18±0.012
F3	22.32±0.240	0.61±0.035	0.72±0.042	15.27±0.63	1.18±0.016
F4	26.52±0.230	0.53±0.029	0.67±0.032	20.80±0.54	1.26±0.012
F5	21.20±0.236	0.65±0.024	0.78±0.024	16.66±0.23	1.2±0.002
F6	22.72±0.101	0.51±0.029	0.64±0.034	20.30±0.74	1.25±0.023
F7	24.17±0.408	0.70±0.026	0.81±0.031	13.50±0.21	1.15±0.341
F8	23.78±0.221	0.56±0.057	0.63±0.057	11.11±0.89	1.12±0.037

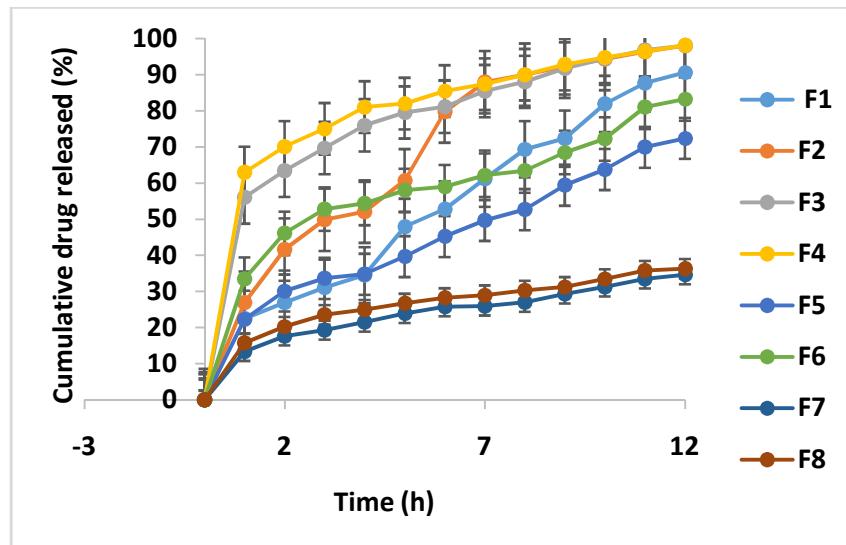
All values mentioned as mean ±SD; The number of trials (n)=3

Table 3. Results of Post-compressional parameters of the prepared mini-tablets

Formulation	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	%Drug content
F1	59.20±0.87	2.77±0.110	3.00±0.50	0.45±0.01	96.77±0.44
F2	44.52±0.70	2.98±0.065	2.90±0.30	0.28±0.04	98.73±0.93
F3	61.21±0.82	3.23±0.134	3.10±0.40	0.68±0.03	97.51±0.27
F4	46.12±1.03	2.77±0.114	3.08±0.12	0.49±0.06	96.88±0.96
F5	59.78±0.34	3.01±0.071	2.80±0.19	0.26±0.07	96.87±0.85
F6	46.01±1.26	2.81±0.026	3.06±0.20	0.58±0.01	97.53±0.82
F7	58.23±0.96	2.94±0.026	3.00±0.12	0.39±0.08	98.73±0.73
F8	44.19±0.84	2.87±0.010	3.38±0.18	0.47±0.07	97.78±0.82

All values mentioned as mean ±SD; The number of trials (n)=3

The drug release from formulated tablets was shown in Fig.3. This dissolution was treated with kinetic modeling viz., First order, Korsmeyer Peppas, Higuchi and Hixson Crowell modeling. The graphs were represented in Fig 4 to 7. The best formulation was subjected to accelerated stability studies as per ICH guidelines. The formulated tablets did not show any changes in all the characters before and after stressed storage conditions (Table 4).

**Fig. 3. Zero order Plots of Formulations**

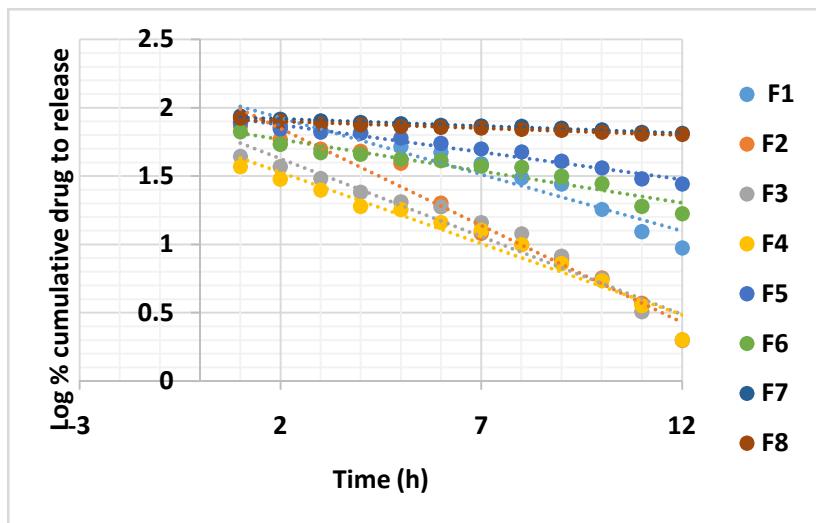


Fig. 4. First order Plots of Formulations

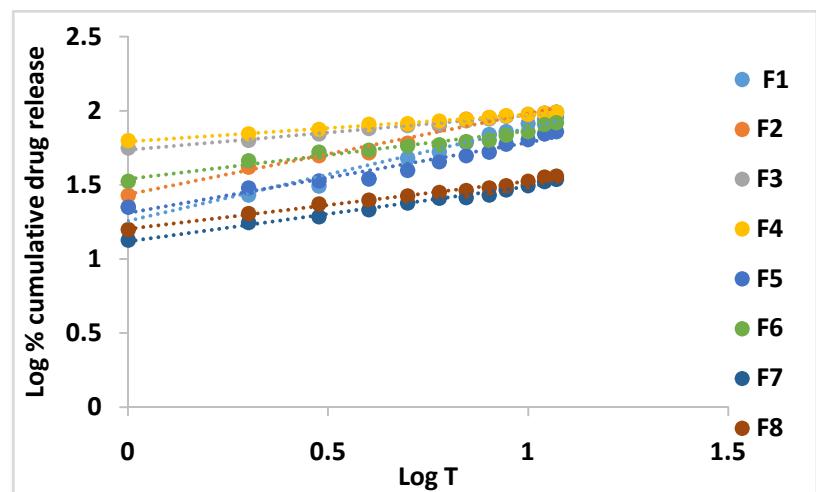


Fig. 5. Korsmeyer Peppas Plots of Formulations

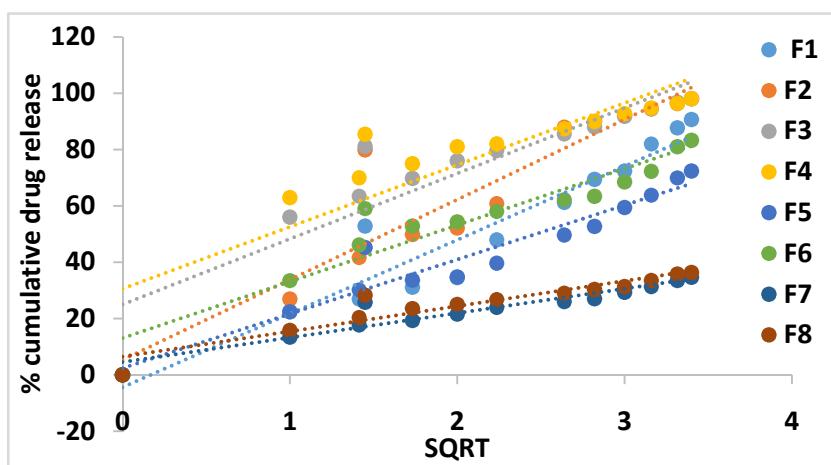
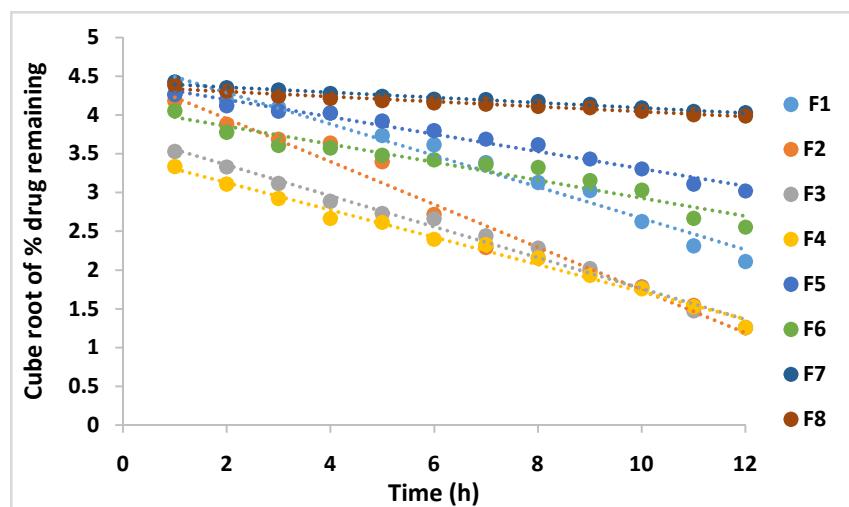


Fig. 6. Higuchi's Plots of Formulations

**Fig. 7. Hixson Crowell's plots of Formulations****Table 4: Selected Formulation (F2) for Stability Studies (stored at 40°C/75% RH)**

Parameter	Before stability studies	After stability studies
General Appearance	White round	White round
Thickness (mm)	2.98±0.065	2.98±0.065
Hardness (kg/cm ²)	2.90±0.30	2.90±0.30
Friability (%)	0.28±0.04	0.28±0.04
Weight (mg)	44.52±0.70	44.52±0.70
Drug Content (%)	98.73±0.93	No change in drug content
In vitro drug release at 12 th h (%)	Complete release	Complete release

All values mentioned as mean ± S.D; Number of trials (n) = 3

Conclusion

The study concludes that mini tablets filled hard gelatin capsules can be developed using Hydroxy propyl methyl cellulose and Kollidone for controlled release of drug from the dosage form.

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