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FORMULATION AND IN VITRO EVALUATION OF MEXILETINE HYDROCHLORIDE TIMED RELEASE CAPSULES

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ABSTRACT

The aim of the present work was formulation and *in-vitro* evaluation of Mexiletine hydrochloride 200mg timed- release capsules. Which release the drug at different time intervals in the GI tract. Objective of the work is to formulate timed release dosage form by adopting wet granulation method using synthetic polymers (HPMCE15), Croscormellose sodium and Eudragit L 100 at different ratios. Timed-release capsules of Mexiletine HC1 were successfully prepared using Lactose, HPMC E15 and Eudragit L 100 by wet granulation method. The timed-release capsules were evaluated for pharmacopoeial and non-Pharmacopoeial tests. Based on the results batch F4 was identified as better formulations amongst all formulations for delivering the drug in a pulsatile manner. Mexiletine HC1 release from the developed formulations has been observed to be directly proportional to the amount of polymer present in capsules. Capsules of batch F4 passed all official and unofficial quality control tests. Data obtained from kinetic treatment revealed F_4 formulation follow Higuchi model. Accelerated stability developed formulations were found to be stable.

Keywords: Mexiletine hydrochloride, Evaluation, Formulation.

INTRODUCTION

Most convenient oral drug products such as tablets and capsule are formulated to release the active drug immediately after oral administration to obtain rapid and complete systemic drug absorption. Such immediate release products result in relatively rapid absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drugs pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate- release dosage form [1].

Aim and Objectives of the study:

The aim of the present work was formulation and *in-vitro* evaluation of *Mexiletine hydrochloride* 200mg timed- release capsules. Which release the drug at different time intervals in the GI tract. Objective of the work is to formulate timed release dosage form by adopting wet granulation method using synthetic polymers (HPMCE15), Croscormellose sodium and Eudragit L 100 at different ratios.

Mexiletine Hydrochloride was selected as a drug due to its low biological half life [2] it requires frequent administration, hence timed release dosage form are formulated to reduce the dosing frequency thereby improving patient compliance.

1. To develop the timed release dosage form of the drug.
2. To perform drug: excipient compatibility studies.
3. To determine the drug content of the different granules of various dosage form.
4. To evaluate parameters such as morphology of the granules, particle size.
5. To reduce the systemic side effects, and to improve the patient compliance. It is delivered through timed-release dosage form.
6. To conduct the *in vitro* release studies for the dosage form.

In case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effects.

In case of *Mexiletine hydrochloride*, it is advised to divide the daily dose of 600-800mg into three does which

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are given at different time intervals. This is done to reduce the adverse effect as well as it has been reported that clinical outcomes are better when three divided doses are given.

Hence a timed-release dosage form of *mexiletine hydrochloride* will be investigated to deliver the doses at different time intervals in a pulsatile manner. Instead of taking three doses at three different time intervals per day, the patient will have to take two timed release capsule leading to better patient compliance.

MATERIALS AND METHODS

Preformulation Studies:

Preformulation is the first step in the rationale development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to formulator in developing stable and bioavailable dosage forms which can be mass-produced.

Identification of pure drug: Identification of *Mexiletine HC1* was carried out by Infrared Absorption Spectrophotometry.

Melting point determination: Melting point of *Mexiletine HC1* was determined by Open capillary method.

UV Spectroscopy:

The first step in preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in the ultraviolet wavelengths (200-400nm), since they are generally aromatic or contain double bonds.

Preparation of the sample for UV analysis

10mg of Mexiletine HC1 was accurately weighed on a microbalance and dissolved in 10ml water (=1000mcg/ml). Water is UV transparent and a good solvent for most polar and non-polar drugs. 1ml of this solution was diluted with 100ml of pH 1.2, pH6.8 and pH7.4 (=10mcg/ml) in separate volumetric flask and scanned on a UV scanner between 200 to 400nm. The maxima obtained in the graph were considered as λ_{max} for the pure drug at respective buffers.

Calibration curves

Experimental methods

Sodium hydroxide solution, 0.2M: Eight grams of sodium hydroxide was dissolved in distilled water and diluted to 1000 ml with distilled water.

Potassium dihydrogen phosphate solution, 0.2 M: Potassium dihydrogen phosphate (27.218 g) was dissolved in distilled water and diluted to 1000 ml.

Hydrochloric acid solution, 0.1 N: Concentrated hydrochloric (8.5 ml) acid was diluted with distilled water and volume was made up to 1000 ml with distilled water. pH (1.2) was adjusted with dilute hydrochloric acid.

Phosphate buffer solution, pH 6.8: Potassium dihydrogen phosphate, 250 ml of 0.2 M, was placed in a 1000 ml volumetric flask, 112 ml of 0.2 M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 6.8 with dilute sodium hydroxide.

Phosphate buffer solution, pH 7.4: Potassium dihydrogenphosphate, 250 ml of 0.2M, was placed in a 1000 ml volumetric flask, 195.5 ml of 0.2M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 7.4 with dilute sodium hydroxide.

Analytical Methods

Preparation of calibration curve in water:

An accurately weighted amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of water, in 100 ml volumetric flask and the volume was adjusted to 100 ml with water (stock I). Form stock I 5ml of solution is transferred to 50 ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 2 µg/ml of Mexiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against water buffer as blank.

Preparation of calibration curve in 1.2pH buffer:

An accurately weighted amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of 1.2 buffer, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 1.2 pH buffer (stock I). From stock I 5ml of solution is transferred to 50ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 25µg/ml of Mexiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against 1.2 pH buffer as blank.

Preparation of calibration curve in 7.4 pH buffer:

An accurately weighed amount of Mexiletine HC1 equivalent to 100 mg was dissolved in small volume of buffer, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 7.4 pH buffer (stock I). From stock I 5ml of solution is transferred to 50 ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 25µg/ml of Mexiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against 7.4 pH buffer as blank.

Preparation of calibration curve in 6.8 pH buffer:

An accurately weighed amount of Mexiletine HC1

equivalent to 100 mg was dissolved in small volume of buffer, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 6.8 pH buffer (stock I). From stock I 5ml of solution is transferred to 50 ml volumetric flask (stock II). A series of standard solution containing Beer-Lambert's range of concentration from 5 to 25µg/ml of Maxiletine HC1 were prepared from stock II and absorbance was measured at 262 nm spectrophotometrically against 6.8 pH buffer as blank,

Formulation development by Granules preparation:

Granules preparation is done by wet granulation method.

All the ingredients including drug and polymer, and excipients are weighed accurately according to formula mentioned in table 1 to 6. All the ingredients are passed through a 24mesh sieve. Required quantity of drug, diluents and polymers are mixed thoroughly sufficient qty of binding agent polyvinyl pyrrolidine added slowly. After enough cohesiveness mass was obtained, the mass was sieve through a 16mesh sieve. The granules were dried at 50˚c for 45 minutes and were blended with magnesium stearate and talc.

Evaluation of granules:

Prepared granules were evaluated for the following parameters [3-5].

Angle of repose:

The angle of repose of the powder blend was determined by using funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the cone was measured and angle of repose was calculated by using the equation,

$\theta = \tan^{-1} h/r$

where,

h = height of the cone

r = radius of the cone

Flow properties for different values of angle of repose were given below.

Bulk density:

An amount of powder blend was introduced in a 100 ml measuring cylinder. Then the weight of powder blend was determined by subtracting the weight of empty measuring cylinder from final weight of measuring cylinder. The cylinder was allowed to fall onto a hard surface from a height of 2.5 cm at 2 sec intervals. The tapping was continued till no volume change noted. Bulk density was calculated by using the formula;

$$\text{Bulk density} = \frac{\text{Mass(gm)}}{\text{Volume(ml)}}$$

Tapped density:

Now this cylinder was put in the holder of USP tapped density apparatus where it was tapped at an average rate of 300 drops / minute, for 500 taps. After 500 taps volume of powder (V_0) was noted and again tapped for another 750 taps. This gave a new volume (V_f). If the difference between v_0 and v_f was more than 2% another 1250 taps are given repeatedly until the difference reduces to less than 2%.Tapped density was found out from following equation:

$$\text{Tapped density} = \frac{\text{Mass(gm)}}{\text{Tapped volume(ml)}}$$

Compressibility index: The compressibility of the powder was determined by the Carr's compressibility index.

$$\text{Carr's index} = \frac{\text{Tapped bulk destiny} - \text{Loose bulk density}}{\text{Tapped volume (ml)}} \times 100$$

Hausner's ratio:

Hausner's ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula:

Hausner's ratio = Tapped density/ Bulk density

Drug content uniformity:

In 100 ml volumetric flask 750mg equivalent weight of granules are taken and dissolved in small quantity of water and the volume was made up to mark with pH 7.4 buffer and stirred for 12 hrs. After stirring the solution was filtered through whatman filter paper and from the filtrate dilutions were made and absorbance was measured spectrophotometrically at 262nm.

Drug polymer interaction:

FT-IR spectra of physical mixture of Mexiletine HC1+Lactose, Mexiletine HC1+Croscarmellose sodium, Mexiletine HC1+PVPk, Mexiletine HC1+Hpmc E15, mexilitine HC1+Eudragit L 100, Mexiletine HC1+Mg.Sterate were determined by using KBr pellet technique. Samples were scanned over the 4000-400cm^{-1}. Spectral region at resolution of 4cm^{-1}. These studies are done to ensure no interaction has been occurred between the drug and polymer.

Data analysis:

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as

1) Cumulative percentage drug released v/s time(In-vitro drug release profile)
2) Cumulative percentage drug released v/s Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining v/s time (First order release)
4) Log percentage drug released v/s log time (Peppas plots) [6].

***In-vitro* release profile:**

Dissolution studies were carried out by using USP Type-1 dissolution test apparatus (Basket) method. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hrs (since the average gastric emptying time is 2 hrs) then removed and the fresh pH 7.4 phosphate buffer saline (PBS) was added. After 6 hrs (average small intestinal transit time is 6 hrs) the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hrs. 900ml of the dissolution medium was used at each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5˚C five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 262 nm, by UV absorption spectroscopy.

Higuchi's Release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$F = K.t^{1/2}$

Where, 'F' is the amount of drug release,

'K' is the release rate constant, and

't' is the release time.

When the data is plotted as accumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer and Peppas Release model:

The release rate data were fitted to the following equation,

$M_t/M\infty = K.t^n$

Where, $M_t/M\infty$ is the fraction of drug release,

'K' is the release constant,

't' is the release time,

'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

When the data is plotted as Log of drug released versus Log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from Y – intercept.

Zero Order Release Rate Kinetics:

To study the zero-order release kinetics the release rate date are fitted to the following equation.

$F = K.t$

Where 'F' is the fraction of drug release, 'K' is the release rate constant and 't' is the release time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

Accelerated stability studies:

Stability studies for the optimized formulation were carried out at 40±2˚c/75±5% RH for 6weeks. Stability studies were carried out using Thermo lab stability chamber. After 4weeks the optimized formulation was tested for physical appearance, drug content and DSC.

RESULTS

PREFORMULATION STUDIES

Infrared spectroscopy:

The drug is identified as a mexiletine hydrochloride by the observation of peaks in the following region cm^{-1} 2590, 1616, 850, 1487, 1616 which is compared to the standard.

Melting point determination:

Melting point of Mexiletine HC1 was determined by **Open capillary method.** The results are tabulated in the table 9.

By comparing to the standard melting point which is found to be $203\text{-}205^0$c (drug bank DBOO379) it is more or less equal to the standard.

UV Spectroscopy:

UV scanning of the drug revealed that the drug had λmax of 262 nm in distilled water. Also, the IR spectrum was concordant with the reference spectrum of Mexiletine hydrochloride.

Calibration curves

Calibration curve has been drawn using different solutions like water and buffers 1.2, 6.8, 7.4.

From the standard curve of mexiletine hydrochloride,it was observed that the drug obeys Beer-Lambert's law in concentration range of 5-25µg/ml in water. The linear regression equation generated was used for the calculation of amount of drug.

Drug and polymer compatibility

Infrared analysis has been carried out to check the polymer compatibility with the polymers.Physical mixture of drug and polymer was characterized by FT-IR & DSC spectral analysis for any physical as chemical alteration of the drug characteristics. From the result it was concluded that there was no interference of the functional groups as the principal peaks of the mexiletine hydrochloride were found to be unaltered in the spectra of the drug-polymer physical mixture. And its wave number has been given in the following table.

Evaluation of granules

Six formulations of matrix granules were prepared (F1 to F6) by using various polymers such as HPMC E15 and Eudragit L100 in different ratios. The granules were prepared by wet granulation method.

Pre compression evaluation

Carr's compressibility index was found to be less than 20% for all the formulations indicating that the powder is compressible. Bulk density and true densities were found to be <1 for all formulation powders. The result of Angle

repose studies and Hausner's ratio indicated that, the powders of all the formulations have free flow and easily compressible.

Drug content uniformity:

In these all the formulations the percentage of drug release has been mentioned in the table 5.7

The drug content uniformity was found to be 93.3 w/w%.

Post compression evaluation

In-vitro drug release studies were carried out in dissolution test apparatus type-1 basket, in 900ml of 0.1 N HC1 for first 2hrs, 900ml of phosphate buffer pH7.4 up to 6.8 up to 4hrs and drug release was found to be up to 93.3% in 12hrs. Based on the results of *in-vitro* release studies F4 was selected as optimized formulation in this formulation HPMC E15 is used 40mg and Eudragit L100 in 60 mg more than this amount the drug shows release at the faster rate . due to the various physiochemical properties of HPMCE15. , HPMC E 15 LV was added in all five formulations (F_1-F_6) to improve the perfection and quality of the coating. The purpose of incorporation HPMC E 15 LV to the coating was to improve the physicochemical property of the coating film, such as ductility, toughness and elasticity. [7,8]. Such film may provide expected controlled release of the drug in the small intestine by offering the increased permeability properties of the fluids present in the colon [9,10]. Coating with polymer solution more than this concentration was found to be problematic, and significant tablet agglomeration was experienced during coating because of the thermoplasticness and tackiness of the Eudragit coating system.

Kinetic release models of optimized formulation

To analyse the mechanism of the drug release rate kinetics of the mexilrtine hydrochloride given in the table 5.15, the data obtained were graphed as

1) Cumulative percentage drug released v/s time(*In-vitro* drug release profile)
2) Cumulative percentage drug released v/s Square root of time (Higuchi's plots)
3) Log cumulative percentage drug remaining v/s time (First order release)

Log percentage drug released v/s log time (Peppas plots) [6].

RELEASE MODEL KINETICS DISCUSSION

However, the curve fitting investigations of the release profile gave us useful insight into the mechanism of drug release from the capsule. The release of the drug from the capsule was controlled. The R^2 value of the data obtained from the capsule is the first Order. The release predicts that the drug follows Higuchi model the value of R^2 is 0.997. Investigated formulations were having timed-release profile; therefore keeping in view all the evolutions, F4 was selected. It was expected such a suitable formulation would be useful to achieve the timed-release profile.

Stability studies

Stability studies were carried out using Thermo lab stability chamber. After 4weeks the optimized formulation was tested for physical appearance, drug content and DSC.

Table 1. Formulation of F1

Formulation ingredients	Granule composition-1	Granule composition-2	Granule composition-3
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	20mg	-
Eudragit L 100	-	-	40mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 2. Formulation of F2

Formulation ingredients	Granule composition-1	Granule composition-2	Granule composition-3
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	25mg	-
Eudragit L 100	-	-	60mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 3. Formulation of F3

Formulation ingredients	Granule composition-1	Granule composition-2	Granule composition-3
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	30mg	-
Eudragit L 100	-	-	60mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 4. Formulation of F4

Formulation ingredients	Granule composition-1	Granule composition-2	Granule composition-3
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellosesodium	8mg	-	-
HPMC E15	-	40mg	-
Eudragit L 100	-	-	60mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 5. Formulation of F5

Formulation ingredients	Granule composition-1	Granule composition-2	Granule composition-3
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	60mg	-
Eudragit L 100	-	-	80mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 6. Formulation of F6

Formulation ingredients	Granule composition-1	Granule composition-2	Granule composition-3
	(pH1.2granules)	(pH 6.8granules)	(pH 7.4granules)
Mexiltine HC1	200mg	200mg	200mg
Lactose	40mg	-	-
Croscarmellose sodium	8mg	-	-
HPMC E15	-	80mg	-
Eudragit L 100	-	-	1 00mg
PVP K	1%	1%	1%
Magnesium stearate	5mg	5mg	5mg
Talc	5mg	5mg	5mg

Table 7. Flow property of powders according to angle of repose

Angle of Repose (θ degrees)	Flow property
<25	Excellent
25 - 30	Good
30 - 40	Passable
>40	poor

Table 8. Grating of powders according to Carr's index

Compressibility index	Flow property
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very poor

Table 9. Melting point determination of Mexiletine hydrochloride

Trail1	Trail2	Trail3	Average
199°c	201°c	202°c	201°c

Table 10. Interpretation data of IR Analysis

Wave number	Functional group	Peaks observed in cm^{-1}	Drug	Polymers	Interaction
2450-2700	C-N	2590	YES	YES	NO
1250-1750	C=O	1616	YES	YES	NO
900-675	C-H	850	YES	YES	NO
1500-1400	C-C	1487	YES	YES	NO
1600-1700	N-H	1616	YES	YES	NO

Table 11. Evaluation parameters of Mexiletine HC1 matrix granules

Formulation	Angle of repose(degree)	Bulk density	Tapped density	Compressibility index	Hausner's ratio
F1	27.23°	0.596	0.748	18.45	1.289
F2	28.36°	0.623	0.736	17.95	1.245
F3	26.46°	0.601	0.740	18.98	1.356
F4	28.76°	0.612	0.750	18.36	1.225
F5	29.21°	0.589	0.725	18.65	1.198
F6	29.56°	0.623	0.745	18.24	1.244

Table 12. Drug content uniformity of matrix granules

Formulation	% Cumulative drug release
F1	86.6%
F2	88.0%
F3	87.3%
F4	93.3%
F5	85.3%
F6	84.0%

Post Compression evaluation:

***Invitro* release profile:**

Table 13. Dissolution profile of formulation of F1

Time	absorbance	C in mcg	C in V Made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log %CD released	Log %CD Retained
5	0.063	5.72727	0.057273	51.545	0	0	51.54545	25.77273	74.227	1.41116	1.8705635
10	0.089	8.09091	0.080909	72.818	0.0573	0.057273	72.87545	36.43773	63.562	1.561551	1.8031994
20	0.095	8.63636	0.086364	77.727	0.0809	0.138182	77.86545	38.93273	61.067	1.590315	1.7858085
30	0.11	10	0.1	90	0.0864	0.224545	90.22455	45.11227	54.888	1.654295	1.7394752
40	0.114	10.3636	0.103636	93.182	0.1	0.324545	93.59727	46.79864	53.201	1.670233	1.7259228
50	0.12	10.9091	0.109091	98.182	0.1036	0.428182	98.61	49.305	50.695	1.692891	1.7049651
60	0.128	11.6364	0.116364	104.73	0.1091	0.537273	105.2645	52.63227	47.368	1.721252	1.6754825
120	0.132	12	0.12	108	0.1164	0.653636	108.6536	54.32682	45.673	1.735014	1.6596613
180	0.022	1.46667	0.014667	13.2	0	0	13.2	6.6	93.4	0.819544	1.9703469
240	0.024	1.6	0.016	14.4	0.0147	0.014667	14.41467	7.207333	92.793	0.857775	1.9675137
300	0.013	0.86667	0.008667	7.8	0.016	0.030667	7.830667	3.915333	96.085	0.592769	1.9826541
360	0.014	0.93333	0.009333	8.4	0.0087	0.039333	8.439333	4.219667	95.78	0.625278	1.9812763
420	0.02	1.33333	0.013333	12	0.0093	0.048667	12.04867	6.024333	93.976	0.779909	1.9730154

480	0.022	1.46667	0.014667	13.2	0.0133	0.062	13.262	6.024333	93.369	0.821579	1.9702027
540	0.002	2	0.02	18	0	0	18	9	91	0.954243	1.9590414
600	0.016	1	0.01	9	0.02	0.02	9.02	4.51	95.49	0.654177	1.9799579

Table 14. Dissolution profiles of formulation of F2

Time	Absorbance	Cin mcg	Cin V made up	Cin D.M	Loss	CLA	CDR	%CDR	C% D Retained	Log% CD Released	Log % CD Retained
5	0.056	5.09091	0.050909	45.81818	0	0	45.81818	22.90909	77.0909	1.36008	1.8870032
10	0.064	5.8181	0.058182	52.36364	0.050909	0.050909	52.41455	26.20727	73.7927	1.418422	1.8680136
20	10.088	8	0.08	72	0.05818	0.109091	72.10909	36.05455	63.9455	1.55696	1.8058097
30	0.11	10	0.1	90	0.08	0.18991	90.18909	45.09455	54.9055	1.654124	1.76396155
40	0.121	11	0.11	99	0.1	0.289091	99.28909	49.64455	50.3555	1.695872	1.7020465
50	0.13	11.8182	0.118182	106.3636	0.11	0.3990914	106.7627	53.38136	46.6186	1.72739	1.6685596
60	0.136	12.3636	0.1253636	111.2727	0.118182	0.517273	111.79	55.895	44.105	1.747373	1.6444878
120	0.1478	12.8182	0.128182	115.3636	0.123636	0.640909	116.0045	58.00227	41.9977	1.763445	1.6233258
180	0.09	6	0.06	54	0	0	54	27	73	1.43136	1.86332
240	0.085	5.66667	0.056667	51	0.06	0.06	51.06	25.53	74.47	1.407051	1.8719814
300	0.08	5.33333	0.053333	48	0.056667	0.116667	48.11667	24.05833	75.9417	1.396303	1.8820405
360	0.079	5.26667	0.052667	47.4	0.053333	0.17	47.57	23.785	76.215	1.376303	1.88204058
420	0.06	4	0.04	36	0.052667	0.222667	36.22267	18.11133	81.8887	1.25795	1.9132238
480	0.058	3.86667	0.038667	34.8	0.04	0.262667	35.06267	17.563133	82.4687	14.243815	1.916289
600	0.007	7	0.07	63	0.09	0.09	63.09	31.545	68.454	1.498931	1.8628467
660	0.006	6	0.06	54	0.07	0.16	54.16	27.08	72.92	10432649	1.8628467

Table 15. Dissolution profiles of formulation of F3

Time	Absorbance	CONC (mcg)	C in V made up	C in disso medium	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.054	4.909091	0.04909091	44.18182	0	0	44.18182	22.09091	77.909	1.3442136	1.8915881
10	0.062	5.636364	0.05636364	50.72727	0.049091	0.049091	50.77636	25.38818	74.612	1.0406316	1.8728076
20	0.082	7.454545	0.07454545	67.09091	0.56364	0.105455	67.19636	33.59818	66.402	1.5263158	1.82218
30	0.09	8.181818	0.081818	73.63636	0.074545	0.18	73.81636	36.90818	63.092	1.5671227	1.799973
40	0.099	9	0.09	81	0.081818	0.261818	81.26182	40.63091	59.369	1.6088565	1.7735604
50	0.105	9.545455	0.09545455	85.90909	0.09	0.351818	86.26091	43.13045	56.87	1.6631525	1.7320573
60	0.112	10.18182	0.10181818	91.63636	0.095455	0.447273	92.08364	46.04182	53.958	1.6631525	1.7320573
120	0.12	10.90906	0.10909091	98.18182	0.101818	0.549091	98.73091	49.36545	50.635	1.6934231	1.7044469
180	0.05	3.333333	0.03333333	30	0	0	30	15	85	1.760913	1.9294189
240	0.059	3.933333	0.03933333	35.4	0.033333	0.033333	35.43333	17.71667	82.283	1.248382	1.9153119
300	0.065	4.333333	0.04333333	39	0.039333	0.072667	39.07267	19.53633	80.464	1.2908431	1.9055998
360	0.072	4.8	0.048	43.2	0.043333	0.116	43.316	21.658	78.342	1.3356183	1.8939947
420	0.08	5.333333	0.05333333	48	0.048	0.164	48.164	24.082	75.918	1.3816926	1.8803448
480	0.085	5.666667	0.05666667	51	0.053333	0.217333	51.21733	25.60867	74.391	1.408387	1.8715223
520	0.005	5	0.05	45	0	0	45	22.5	77.5	1.3521825	1.8893017
580	0.003	3	0.03	27	0.05	0.05	27.05	13.525	86.475	1.1311373	1.9368906
640	0.002	2	0.02	18	0.03	0.08	18.08	9.04	90.96	0.9561684	1.9588505

Table 16. Dissolution profiles of formulation of F4

Time	Absorbance	C in mcg	C in V made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.059	5.363636	0.0536364	48.27273	0	0	48.27273	24.13636	75.86364	1.3826718	1.88003366
10	0.068	6.181818	0.0618182	55.63636	0.053636	0.053636	55.69	27.845	72.155	1.4447472	1.85826643
20	0.084	7.636364	0.0763636	68.72727	0.061818	0.115455	68.84273	34.42136	65.57864	1.5368281	1.85826643
30	0.091	8.272727	0.0827273	74.45455	0.076364	0.191818	74.64636	37.32318	62.67682	1.5719787	1.79710694
40	0.1	9.090909	0.0909091	81.81818	0.82727	0.274545	82.09273	41.04636	58.95364	1.6132747	1.7705106
50	0.11	10	0.1	90	0.090909	0.365455	90.36545	45.18273	54.81727	1.6549724	1.7389174
60	0.115	10.45455	0.1045455	94.09061	0.1	0.465455	94.55636	47.278181	52.72182	1.67466608	1.72199038
120	0.121	11	0.11	99	0.104545	0.57	993.57	49.785	50.215	1.6970985	1.70083347
180	0.057	308	0.038	34.2	0	0	34.2	17.1	82.9	1.2329961	1.91855453
240	0.067	4.466667	0.0446667	40.2	0.038	0.038	40.238	20.119	79.818	1.3036064	1.90244349
300	0.075	5	0.05	45	0.044667	0.082667	45.08267	22.54133	77.45867	1.3529796	1.88907002
360	0.08	5.333333	0.05333333	48	0.05	0.132667	48.13267	24.06633	75.93367	1.3814099	1.88043437
420	0.085	5.666667	0.0566667	51	0.0533333	0.186	51.186	25.593	74.407	1.4081212	1.87161379
480	0.089	5.933333	0.0593333	53.4	0.0566667	0.242667	53.64267	26.82133	73.17867	1.4284804	1.86438449

540	0.009	9	0.09	81	0	0	81	40	60	1.60206	1.77815125
600	0.0077	0.07	63	0.09	0.09	0.09	63.09	31.45	68.55	1.4976206	1.83600746

Table 17. Dissolution profiles of formulation of F5

Time	Absorbance	C in mcg	C in V made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.019	1.727273	0.017273	15.54545	0	0	15.54545	7.772727	92.227273	0.890573	1.9648594
10	0.027	2.454545	0.024545	22.09091	0.017273	0.017273	22.10818	11.05409	88.945909	1.043523	1.949126
20	0.036	3.272727	0.032727	29.45455	0.024545	0.041818	29.49636	14.74818	85.251818	1.168738	1.9307037
30	0.05	4.545455	0.045455	40.90909	0.032727	0.074545	40.98364	20.49182	79.508182	1.31158	1.9004118
40	0.056	5.090909	0.050909	45.81818	0.045455	0.12	45.93818	22.96909	77.030909	1.361144	1.886665
50	0.08	7.272727	0.072727	65.45455	0.050909	0.170909	65.62545	32.81273	67.187273	1.516042	1.827287
60	0.082	7.454545	0.074545	67.09091	0.072727	0.243636	67.33455	33.66727	66.332727	1.527208	1.827279
120	0.085	7.727273	0.07273	69.54545	0.074545	0.318182	69.86364	34.91391	65.068182	.1543221	1.8213687
180	0.038	2.533333	0.025333	22.8	0	0	22.8	11.4	88.6	1.056905	1.9474337
240	0.036	2.4	0.024	21.6	0.025333	0.025333	21.62533	10.81267	89.187333	1.033933	1.9503032
300	0.032	2.13333	0.021333	19.2	0.024	0.049333	19.24933	9.624667	90.375333	0.983386	1.9560499
360	0.036	2.4	0.024	21.6	0.021333	0.070667	21.67067	10.83533	89.164667	1.034842	1.9501928
420	0.03	2	0.02	18	0.024	0.094667	18.09467	9.047333	90.952667	0.956521	1.9588154
480	0.046	3.06667	0.030667	27.6	0.02	0.114667	27.71467	13.85733	86.142667	1.14168	1.9352183
540	0.005	5	0.05	45	0	0	45	22.5	77.5	1.352183	1.8893017
600	0.006	6	0.06	54	0.05	0.05	54.05	27.02	72.98	1.431685	1.8632039
660	0.008	8	0.08	72	0.06	0.06	72.06	36.5	63.95	1.556905	1.8058405
720	0.006	6	0.06	54	0.08	0.08	54.08	27.75	72.925	1.432568	1.8628764

Table 18. Dissolution profiles of formulation of F6

Time	Absorbance	C in mcg	C in V made up	C in D.M	Loss	CLA	CDR	%CDR	C%D Retained	Log% CD Released	Log %CD Retained
5	0.048	4.363636	0.43636	39.27273	0	0	39.27273	19.63636	80.364	1.2930611	1.90506
10	0.058	5.272727	0.052727	47.45455	0.043636	0.043636	47.49818	23.74909	76.251	1.375647	1.882245
20	0.062	5.636364	0.056364	50.27272	0.052727	0.096364	50.82364	25.41182	74.588	1.4050357	1.87267
30	0.067	6.090909	0.060909	54.81818	0.056364	0.152727	54.97091	27.48545	72.515	1.4391029	1.860425
40	0.069	6.272727	0.062727	56.45455	0.060909	0.213636	56.66818	28.33409	71.666	1.4523093	1.855313
50	0.072	6.545455	0.065455	58.90909	0.062727	0.276364	59.18545	29.59273	70.407	1.471185	1.847618
60	0.077	7	0.07	63	0.05455	0.341818	63.34182	31.67091	68.329	1.5006605	1.834606
120	0.081	7.363636	0.073636	66.27273	0.07	0.41818	66.68455	33.34227	66.658	1.5229952	1.823851
180	0.048	0.851613	0.032	28.8	0	0	28.8	14.4	85.6	1.1583625	1.932474
240	0.042	0.745161	0.028	25.2	0.032	0.032	35.232	12.61	.87.39	1.1007151	1.941462
300	0.039	0.691935	0.026	23.4	0.028	0.06	23.46	11.7	88.3	1.0681859	1.945961
360	0.0367	0.656452	0.024	22.2	0.026	0.086	22.286	11.14	88.86	1.0468852	1.948706
420	0.042	0.745161	0.028	25.2	0.024	0.11	25.31	12.65	87.35	1.1020905	1.941263
480	0.05	0.887097	0.033	30	0.028	0.128	30.128	15	85	1.1760913	1.929419
520	0.007	7	0.07	63	0	0	63	31.54	68.46	1.4988617	1.835437
600	0.005	5	0.05	45	0.07	0.07	45.07	22.6	77.4	1.3541084	1.888741
660	0.003	3	0.03	27	0.05	0.12	27.12	13.65	86.35	1.1351327	1.936262
720	0.002	2	0.02	18	0.03	0.15	18.15	9.16	90.84	0.9618955	1.958277

Table 19. Kinetics of drug release of R^2 value for F_4 formulation.

Model Name	K Value	R^2 value
Zero order	1.901	0.969
First Order	-0.010	0.977
Peppas model	0.457	0.990
Higuchi model	9.697	0.997

Table 19. Stability study analysis

Parameters	2^{nd} week	4^{th} week
Physical Appearance	No Change	No Change
Drug content	90.3%	93.3%

Fig 1. Wavelength scans of pure drug

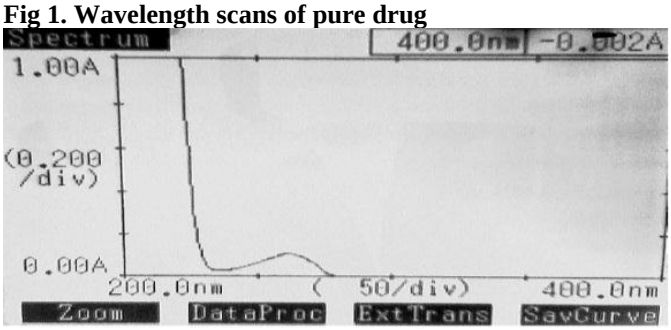


Fig 2. Calibration curve of Mexiletine hydrochloride in water

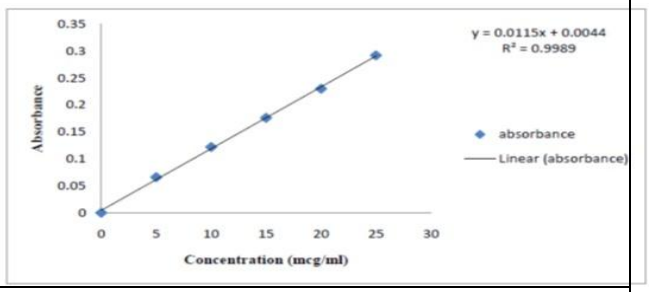


Fig 3. Calibration Curve of Mexiletine HC1 in 1.2 buffer

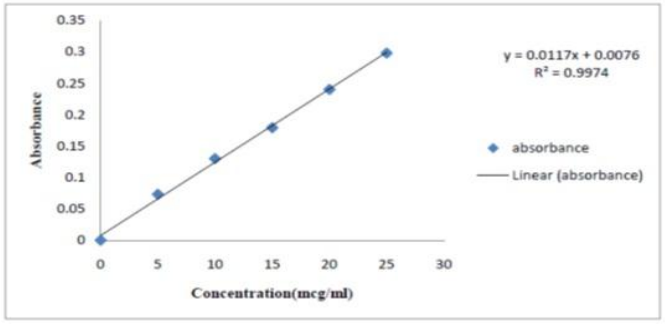


Fig 4. Calibration Curve of Mexiletine HC1 in 7.4 buffer

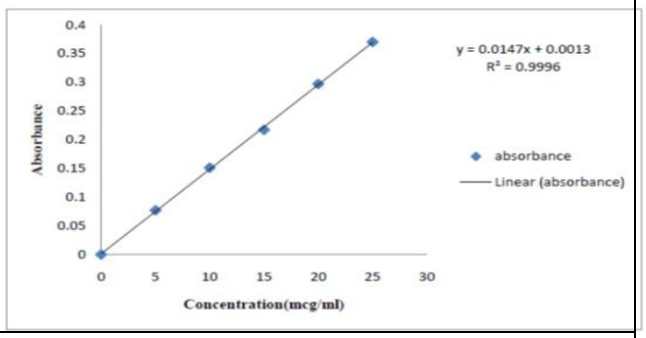


Fig 5. Calibration Curve of Mexiletine HC1 in 6.8 buffer

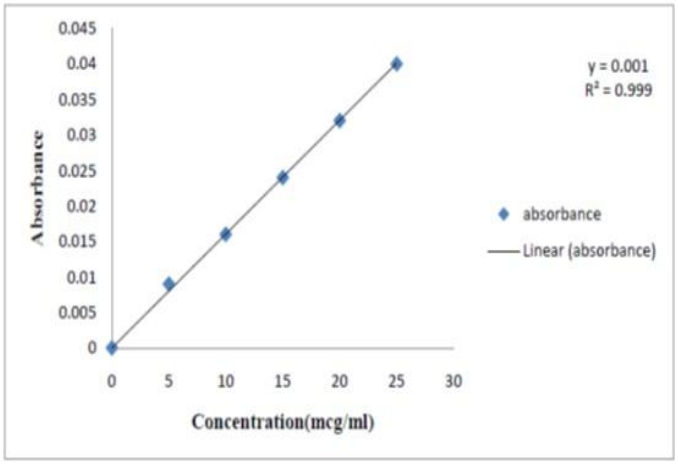


Fig 6. IR spectrum of pure drug

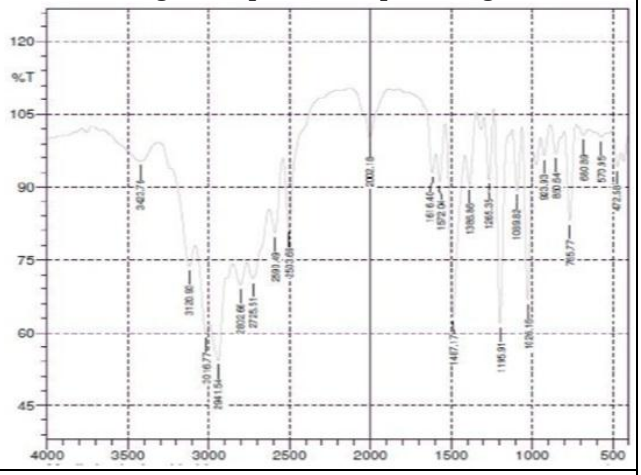


Fig 7. IR spectrum of Drug and Lactose

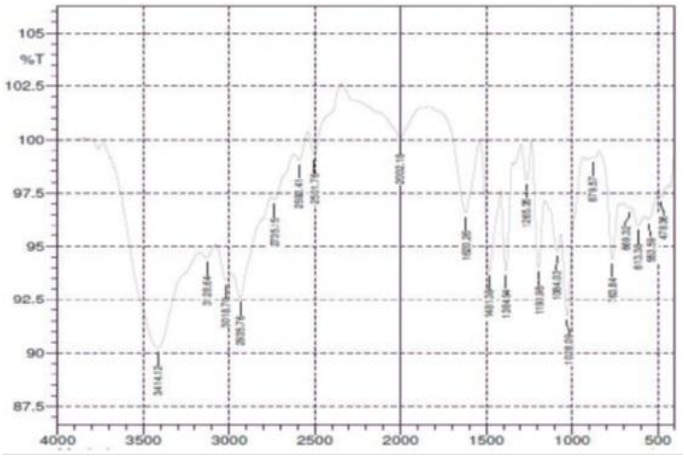


Fig 8. IR spectrum of Drug and Croscarmellose Sodium

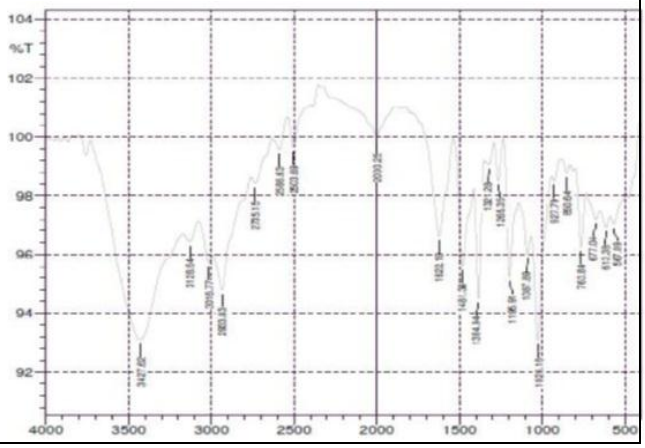


Fig 9. IR spectrum of Drug and HPMC

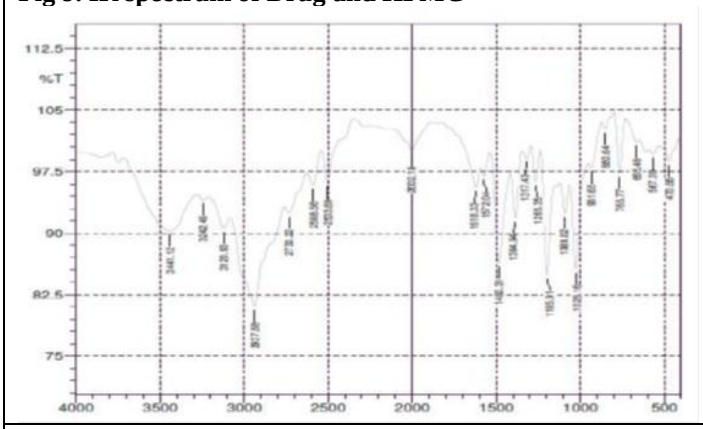


Fig 10. IR spectrum of Drug and PVP-K

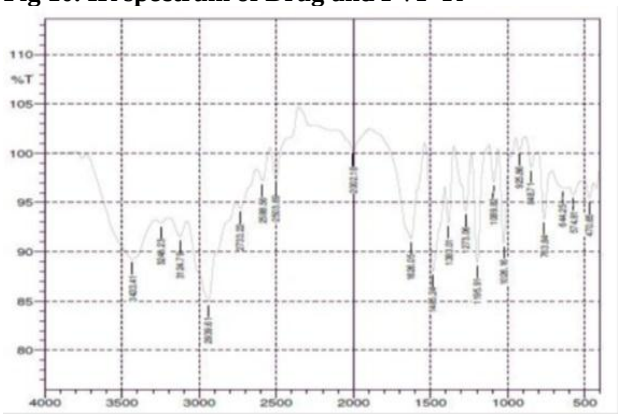


Fig 11. IR spectrum of Drug and Eudragit L 100

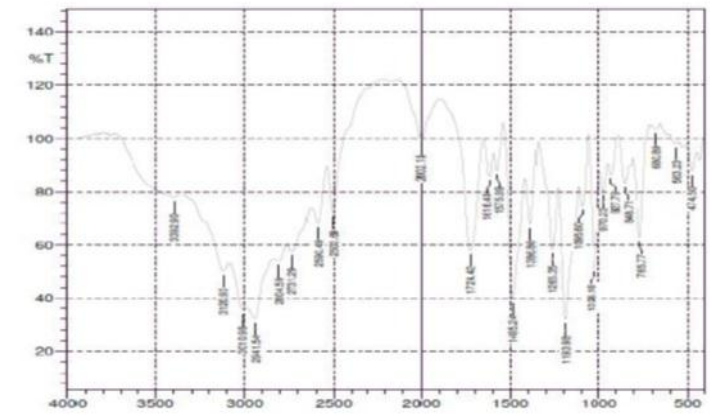


Fig 12. IR spectrum of Drug and magnesium stearate

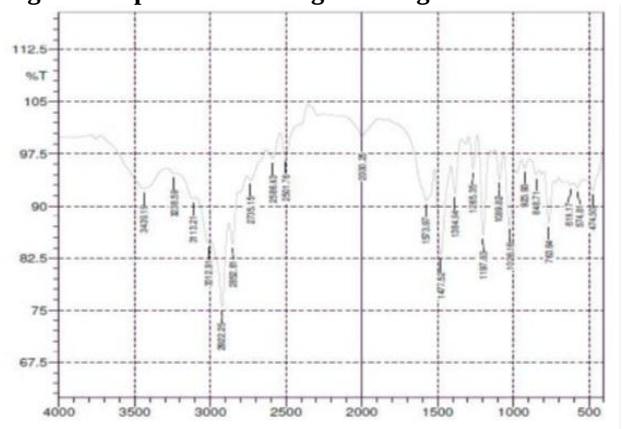


Fig 13. Drug release profiles of formulations of F_1 to F_6

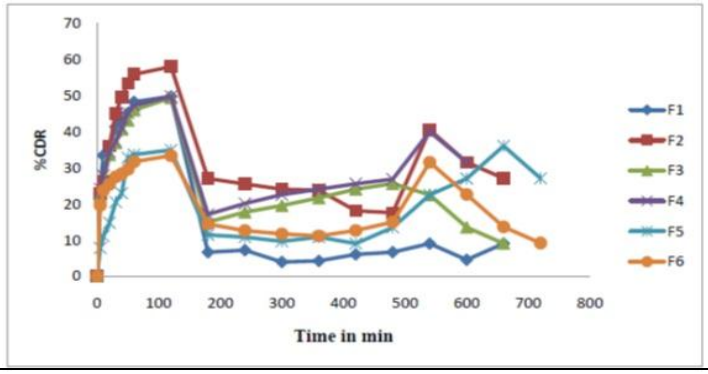


Fig 14. Zero order drug release profiles of optimized formulation

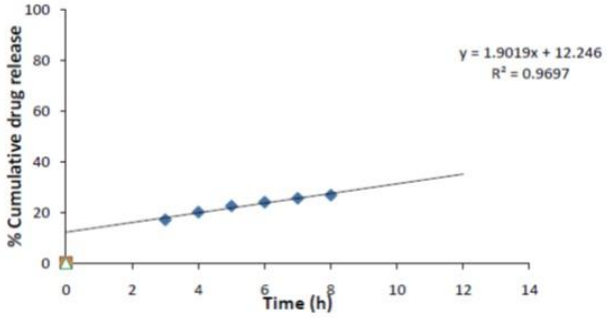


Fig 15. First order comparative dissolution profiles of optimized formulation

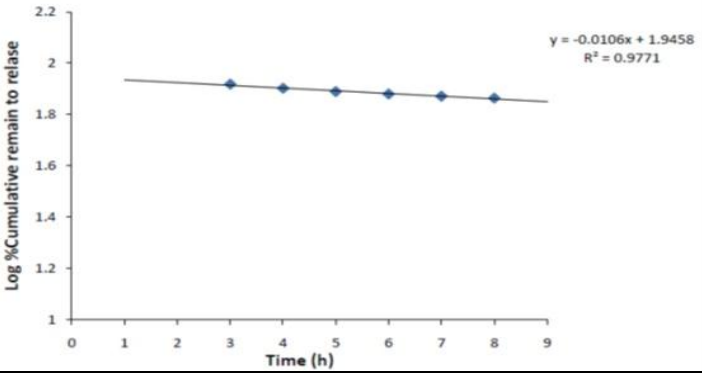


Fig 16. Higuchi comparative dissolution profiles of optimized formulation

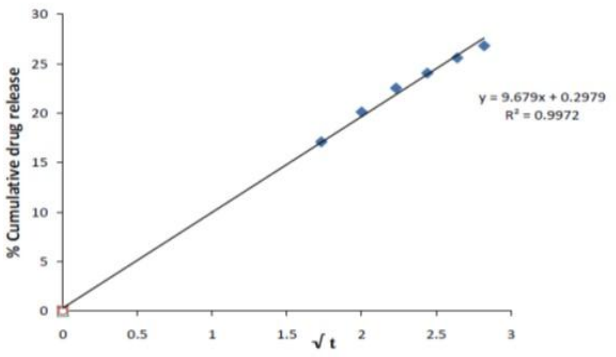


Fig 17. Peppas comparative dissolution profiles of optimized formulation

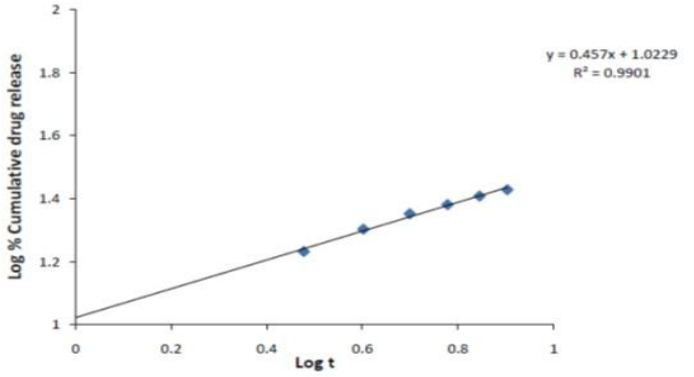
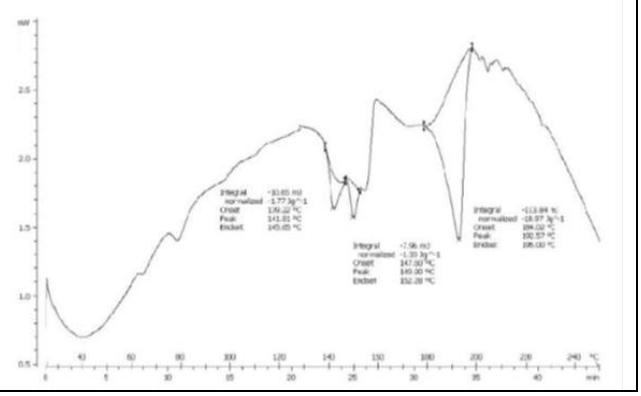


Fig 18. DSC graph of formulation IV after stability studies



DISCUSSION

Granules were kept for accelerated stability study at 40±2◦C and 75±5% RH for 4 weeks in stability chamber. After a period of 4 weeks, the samples were observed for any physical parameters, drug content and DSC. It was observed that there is no change in appearance, drug content and DSC.

A Timed- release delivery system for Mexiletine Hydrochloride was designed to increase its patient compliance by using a suitable polymer. Compared to oral conventional delivery system, the frequency of dosing may be less.

The various pre formulation studies like melting point determination, solubility, and calibration curve of the drug by UV spectroscopy and physico - chemical characteristics of drug have been studied. The results of all these parameters are tabulated and depicted graphically in the result and discussion section.

Six formulations were prepared by using same drug and polymer in different ratios. The granules were prepared by using the wet granulation technique and were subjected to evaluation of granular properties like angle of repose, bulk density, compressibility index and Hausner's ratio.

Evaluation parameters viz. bulk density, angle of repose, drug content Carr's compressibility index was found to be less than 20% for all the formulations indicating that the powder is compressible. Bulk density and true densities were found to be <1 for all formulation powders were within acceptable limits for all six formulation.

Results of *in-vitro* release using USP dissolution apparatus indicated that the drug release of formulation F_4 is satisfactory and others it was found to be 50% - 93.3% for 12 hrs respectively.

The results of kinetic drug release of formulation F_4 in the R^2 value was highest for Higuchi model. Stability study for the granules at 40±2◦C and 75±5% RH for 4 weeks in stability chamber. It was observed that there is no change in appearance, drug content and DSC.

CONCLUSION

The conclusions drawn from the present investigation were given below Suitable analytical method based on UV-Visible spectrophotometer was developed for Mexiletine Hydrochloride. 262 nm was identified as an λmax in purified water. Timed-release capsules of Mexiletine HC1 were successfully prepared using Lactose, HPMC E15 and Eudragit L 100 by wet granulation method. The timed-release capsules were evaluated for pharmacopoeial and non-Pharmacopoeial (industry specified) tests. Based on the results batch F4 was identified as better formulations amongst all formulations for delivering the drug in a pulsatile manner. Mexiletine HC1 release from the developed formulations has been observed to be directly proportional to the amount of polymer present in capsules. Capsules of batch F4 passed all official and unofficial quality control tests. Data obtained from kinetic treatment revealed F_4 formulation follow Higuchi model. Accelerated stability developed formulations were found to be stable.

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