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FORMULATION AND EVALUATION OF CARBAMAZEPINE BILAYER TABLET FOR BIMODAL RELEASE

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ABSTRACT: Carbamazepine (CBZ) has long been a therapeutic option for bipolar disorder. Carbamazepine used for the treatment of acute manic and mixed episodes associated with bipolar I disorder. In the present study bilayer tablet was developed to improve dosing convenience and decrease daily fluctuations in serum CBZ concentration, thereby lowering the incidence of adverse events. In bilayer tablet one layer provided the loading dose by immediate drug release and another layer provided maintenance dose up to 12 hrs by sustained release. The drug excipient compatibility study was carried out by FTIR and DSC techniques, there was no interaction found. Cross povidone was used as superdisintegrant in immediate release layer and controlled release fraction was formulated by using HPMC K 100 polymer. The prepared granules were evaluated for angle of repose, bulk density, tapped density and compressibility index which showed satisfactory result. The prepared bilayer tablets were evaluated for thickness, hardness, friability and *in-vitro* release studies. *In-vitro* dissolution study was carried out for 12 hours using USP dissolution apparatus I using 1.2 pH and 7.4 phosphate buffer as dissolution medium. The bilayer tablet showed initial burst release to provide the loading dose of drug followed by sustained release up to 12 hours. Concentration of polymer and superdisintegrant ratio influenced drug release profile. As the polymer concentration was increased in sustained release layer the % drug release decreased.

INTRODUCTION: For decades, oral medication delivery has been acknowledged as the most extensively used route of administration among all the ways that have been investigated for systemic drug delivery. Any drug delivery system's purpose is to provide a therapeutic amount of medicine to the patient at the right time for the length of treatment and then maintain the desired drug concentration [1].

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The conventional dosage form causes a wide range of drug concentration fluctuations in the bloodstream and tissues, reduced or lost therapeutic effectiveness, as well as an increase in the incidence of adverse effects, which can lead to undesirable toxicity and inefficiency.

Sustained or controlled drug delivery systems, on the other hand, can reduce dosage frequency while also increasing therapeutic effectiveness by localising the drug at the site of action, lowering the dose necessary, and ensuring uniform drug delivery [2]. Bilayer tablet is a new approach for the effective development of sustained release formulations, which includes an instant release (IR) layer and a sustained release (SR) layer.

It has a bimodal drug delivery characteristic (slow release / quick release / slow release) [3]. Even if a dosage form with a zero-order *in-vitro* release is used, a constant plasma concentration may not be achieved. It's feasible that a delivery system that provide a initial burst release followed by a more constant or accelerated release at a later time may be a superior solution. A release profile such as pseudo zero-order release with initial burst or bimodal release may compensate for the lower absorption rate in the stomach and large intestine [4-5].

Based on these considerations, a new oral delivery device in the shape of a double-component tablet has been proposed, with one portion prepared to achieve a rapid release of the medication with the goal of attaining a high serum concentration in a short period of time. The second layer is a prolonged-release layer, which is designed to keep an effective plasma level for a long time. Epilepsy is a neurological disorder in which brain activity becomes abnormal, causing convulsions or periods of unusual behavior, sensations and sometimes loss of awareness. Diseases like epilepsy require immediate release of drug for instant effect to manage the panic attack at its presentation and then drug concentration has to be maintained for prolong effect of the drug [6].

For its anticonvulsant and antineuralgic properties, carbamazepine is employed. This medication's popularity is attributed to a number of positive traits, including its efficacy in managing various seizure types. It has a low bioavailability of less than 70%, irregular oral absorption, and poor water solubility. Additionally, the therapeutic window for carbamazepine is small, and there are variations in its bioavailability. An effort to reduce the frequency of dosing necessary for chronic carbamazepine therapy and to lessen the variability in plasma concentration [7-10]. Hence, in the present study, a bilayer tablet for bimodal drug release in which one layer of immediate release and second layer of sustained release of Carbamazepine was designed.

MATERIAL AND METHOD: Carbamazepine was purchased from Yarrow Chem. Pvt. Ltd. Cross povidone, HPMC K100, starch, lactose, talc, magnesium stearate were purchased from S.D Fines Chem. Ltd., Mumbai. All other ingredients, reagents and solvents were of analytical grade.

Compatibility Studies: The compatibility studies of the drug with polymers are studied using FT-IR and DSC techniques [11-12].

FT-IR Spectroscopy: For the purpose of determining the drug and excipients were compatible, FT-IR spectroscopy was used. A thermal Nicolet FTIR was used for infrared spectroscopy, and the spectrum was collected between 4000 and 400 cm^{-1}. The sample was squashed into discs using a hydraulic press at a pressure of 5 tonnes for 5 minutes using a 1:1 mixture of the drug and excipients in KBr (200-400mg). By looking for any changes in drug peak locations in the spectrum of a physical mixture of drug excipients, the interaction between drug and excipients was discovered by IR spectral investigations.

DSC Analysis for Formulation: Shimadzu Limited's Different Scanning Calorimeter -60 was used to examine the thermal characteristics of both pure drug and the physical mixture of the drug and excipients. In aluminium pans with a thermic seal, the samples were heated. Each sample's heat runs were set between 25 and 350°C with a heating rate of 100°C/min and nitrogen as the blanket gas.

Preparation of Bilayered Tablets of Carbamzepine: The immediate release layer of the tablet was prepared by blending Carbamazepine uniformly with super disintegrant (Cross povidone) as per the formulae given in **Table 1**. The drug-superdisintegrant blend was then mixed with MCC using twin blender for 10 min. The final mass was lubricated with magnesium stearate [13].

The sustained release layer of the tablet was prepared by wet granulation technique by mixing carbamazepine uniformly with different proportions of HPMC-K 100, magnesium stearate and starch as given in the **Table 2**, PVP-K30 was used as a binder. The wet mass was passed through #30 to obtain granules. The granules were dried at 60ºC in a tray drier. The granules of 30 or 60# size were lubricated with magnesium stearate. The bilayer tablet were firstly compressed using rotary tablet press for sustained release layer and then

again compressed with immediate release layer over the sustained release layer.

Evaluation of Powder Blends: Flow properties of powder blend (before compression) were characterized by the bulk density and tapped bulk density, angle of repose, compressibility index (Carr's index), and Hausner's ratio. These tests were repeated 3 times for each formulation [14-15].

Bulk Density: The apparent bulk density (b) was calculated by filling a graduated cylinder with presieved medication excipients blend and measuring the volume (Vb) and weight (M) as

$$\rho b = M/Vb$$

Tapped Density: The measuring cylinder, which contained a known mass of blend, was tapped for a predetermined amount of time. The cylinder's minimum volume (Vt) and the blend's weight (M) were both measured. The following formula was used to compute the tapped density (t).

$$\rho t = M/Vt$$

Compressibility Index: The simplest way of measurement of free flow property of powder is compressibility, with which a material can be induced to flow is given by % compressibility which is calculated as follows:

$$C = (\rho t - \rho b) / \rho t \times 100$$

ρt - tapped density

ρb - untapped bulk density

Hausner's Ratio: Hausner's ratio is an important character to determine the flow property of powder and granules. It is calculated by following formula.

$$\text{Hausner's ratio} = \rho t / \rho b$$

ρt - tapped density

ρb - untapped bulk density

Angle of Repose: Angle of repose is described as the maximum possible angle between the surface of a powder pile or granules and the horizontal plane. The granules were allowed to flow through a funnel fixed to a clamp at a definite height. The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the formed granules heap and putting the values into the equation

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

Compression of Bilayered Tablets: The bilayer tablet of Carbamzepine was prepared using a Rotary Mini tablet press (Shakthi Pvt. Ltd., India) equipped with flat punches. The die was initially filled with the weighed amount sustained release portion and was lightly compressed. Over this compressed layer, the required quantity of the immediate release layer powder mixture was placed and compressed to obtain hardness of the tablet 4–6 kg/cm^2. It was observed that tablet compressed at this force did not show any layer separation. The total weight of the tablet was kept constant, *i.e.*, 600 mg for all formulation.[13]

Evaluation of Bilayer Tablets: The following physicochemical tests were conducted to evaluate the post compressional parameters of the tablet [16-17].

General Appearance: The control of a general appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color.

Immediate release layer: Yellow color

Sustained release layer: White color

Thickness: The homogeneity of tablet size required a certain thickness of tablet. Digital screw gauze was used to determine thickness.

Hardness: In this five tablets were selected randomly and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability Test: Friability test was carried out to evaluate the hardness and stability instantly. 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

% Friability = (Initial weight of tablets - Final weight of tablets) / Initial weight of tablets × 100

Weight Variation: This test was performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analyzed for sample mean and percent deviation. IP limit for weight variation in case of tablets weighing 130 - 324 mg ± 7.5 % and more than 324 mg ± 5%.

Uniformity of Drug Content: 5 tablets were selected randomly, weighed and triturated, a tablet triturate equivalent to 100mg of drug weighed accurately, dissolved in 10 ml of methanol and diluted to 100ml. Further dilutions were done suitably and absorbance was measured at 284nm using UV spectrophotometer.

***In-vitro* Dissolution Studies:** The USP-type I dissolution device operated at 50 rpm for the *in-vitro* dissolution trials. The dissolution medium was pH 1.2 for first 2 hours and pH 7.4 for 12 hours (900 mL) at a temperature of 37^{o}C. At predetermined intervals, an aliquot (5mL) was taken out, and the drug content was measured using a Shimadzu 1800 UV-visible spectrophotometer at 285nm.

Kinetic Analysis of Dissolution Data: The release data were fitted into the zero order, first order, Higuchi equation, and Korsmeyer equation (which is frequently used to characterise drug release behaviour from polymeric systems) in order to explore the mechanism of drug release from the tablets.

RESULTS AND DISCUSSION: A successful attempt was made to formulate Carbamazepine bilayer tablets using crosspovidone as immediate release polymer and HPMC K-100 as release retardants using wet granulation method.

Total three formulations were prepared, composition of each formulation is shown in **Table 1** and **2**. The formulated tablets were characterized for various physicochemical parameters.

TABLE 1: COMPOSITION OF IMMEDIATE RELEASE LAYER OF CARBAMAZEPINE

Ingredients (Immediate release)	Quantity per tablet
Drug	25
Cross Povidone	2.5
Starch Mucilage	8
Magnesium Stearate	1
Talc	1
Lactose	12.5
Amaranth	q.s
Total weight (mg)	50

TABLE 2: COMPOSITION OF SUSTAINED RELEASE LAYER OF CARBAMAZEPINE

Ingredients (Sustained release)	Quantity per tablet		
	F1	F2	F3
Drug	150	150	150
HPMC K-100	2.5	2.5	2.5
Aerosil	4	4	4
Starch	60	60	60
PVP K-30	24	24	24
Magnesium Stearate	12	12	12
Talc	8	8	8
IPA	q s	q s	q s
Lactose	150	150	150
Tartarzine	2	2	2
Total weight(mg)	450	450	450

Drug-Excipient Compatibility Study:

Fourier Transport Infrared Spectroscopy (FTIR): Infra red spectra of drug and excipients were recorded by the KBr disk method and the resulting spectra are shown in **Fig. 1** to **3**. All of the characteristic peaks of carbamazepine are present in the spectrum of the drug-excipient mixture, indicating compatibility between drug and excipients. Spectra confirmed no significant changes in the chemical integrity of the drug. Carbamazepine functional group peaks (N-H) stretch, C=C stretch, C=N stretch, and C-N stretch) were unchanged in all IR spectra and are summarized in **Table 3.** The DSC thermogram of carbamazepine shows a sharp endothermic peak at 196.01°C within 1.0°C, indicating that the sample is in pure form. The peaks for formulations containing Cp and HPMC K 100 showed no

apparent change in the melting endotherms of carbamazepine (193.77°C and 189.34°C) compared to pure drug. This observation further supports the IR spectroscopy results.

This indicates that the stability of the formulation may not be affected and confirms that the drug is compatible with all excipients.

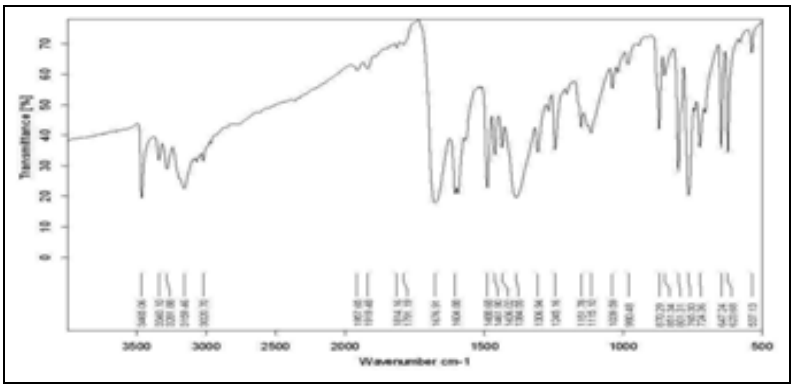

FIG. 1: FTIR SPECTRA OF PURE CARBAMAZEPINE

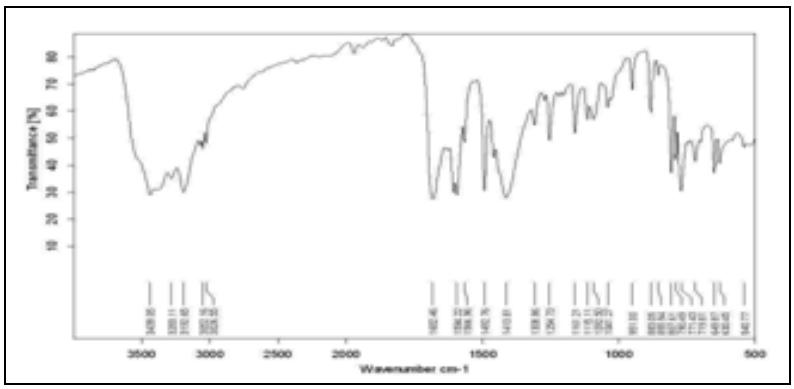

FIG. 2: FTIR SPECTRA OF PHYSICAL MIXTURE OF DRUG AND CROSS POVIDONE

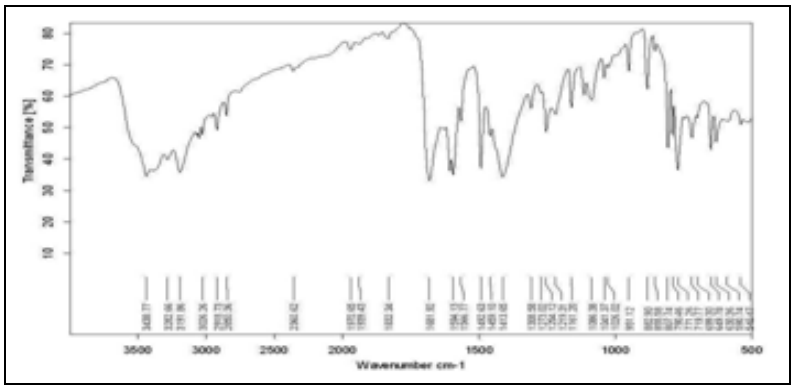

FIG. 3: FTIR SPECTRA OF PHYSICAL MIXTURE OF DRUG AND HPMC

TABLE 3: FTIR SPECTRA OF DRUG AND FORMULATIONS

Codes	N-H Streching	C=C streching	C=N Streching	C-N Streching
Pure Drug	3281.88	3020.70	1676.91	1245.16
Drug with CP	3283.11	3026.55	1682.46	1254.73
Drug with HPMC	3282.66	3026.26	1681.92	1254.12

Evaluation Parameters:

Pre-compressional Parameters:

Bulk Density: The values of bulk density were found to range from 0.4 to 0.44 (IL) and0.534 to 0.54 (SL)

Tapped Density: The values of tapped density were found to range from 0.47 to 0.56 (IL) and 0.566 to 0.6 (SL).

Carr's Consolidation Index: The results of the Carr's consolidation index of all the formulations ranges from 7.1 to 18% (IL) to 5.3 to 10% (SL).

Hausner's Ratio: It was ranging from 1.175 to 1.22 (IL) and 1.05 to 1.11 (SL). Lower the Hausner's ratio better is the flowability, i.e., all the preparation showed that they had good flow properties.

Angle of Repose (θ): The data obtained for angle of repose for all the formulations were tabulated in the **Table 4** and **5**.

All the formulations showed angle of repose value in the range of 16.85 to 19.25 (IL) and 17.7 to 20.25 (SL). The angle of repose value (< 30) indicated good flow properties.

TABLE 4: PRECOMPRESSIONAL PARAMETERS OF IMMEDIATE RELEASE LAYER

Formulation codes	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose Ø
F1	0.4	0.49	18%	1.22	19.25
F2	0.4	0.47	14.80%	1.22	18.92
F3	0.44	0.56	7.10 %	1.175	16.85

TABLE 5: PRE-COMPRESSIONAL PARAMETERS OF SUSTAINED RELEASE LAYER

Formulation codes	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose Ø
F1	0.534	0.59	9.94%	1.11	20.25
F2	0.536	0.56	5.30%	1.05	19.74
F3	0.54	0.60	10 %	1.11	17.7

Post Compression Parameters: Three formulations of carbamazepine were prepared using different concentrations of HPMC K-100, PVP K-30 and cross povidone in different concentration were prepared.

Thickness: The thickness depends on the size of punches and the weight of one tablet (600 mg). The value of thickness ranges between 6.804±0.009 to 7.20±0.015 mm.

Hardness: Hardness of all tablets was maintained within 4 to 6 kg/cm^2. The hardness of all formulations was almost uniform in specific method and possesses good mechanical strength.

Friability (F): Another measure of tablet strength is friability. The values of friability test were given in the **Table 6**.

The % friability for all the formulations was below 1% indicating that the friability was within the prescribed limits the results of friability test indicates that the tablet possesses good mechanical strength.

TABLE 6: POST-COMPRESSIONAL PARAMETERS OF CARBAMAZEPINE BILAYER TABLET

Formulation codes	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	7.12±0.015	5.0±0.152	0.84±0.090	598±0.011	99.25±1.47
F2	6.804±0.009	4.95±0.142	0.81±0.094	606±0.038	98±1.62
F3	7.20±0.015	5.0±0.264	0.83±0.094	597±0.010	98.57±0.28

Weight Uniformity: All the tablets were passed weight variation test as the average weight variation was within the pharmacopoeial limit ±5%. The weight of all the tablets was found to be uniform with low standard deviation value.

Uniformity of Drug Content: The % drug content of carbamazepine in all the formulated tablets were found within the limits. % drug content value of carbamazepine was within 98±1.62 to 99.25±1.475%. The results within the range which indicates uniform mixing of drug.

***In-vitro* Dissolution Study:** *In-vitro* studies were performed to study the drug release from dosage form in the physiological condition and kinetics of drug release. The *in-vitro* drug release profiles of F1-F3 are shown in **Fig. 4** to **7** Three formulations of carbamazepine with HPMC K-100, in different concentration were studied.

It was observed that the controlled type of polymer influences the drug release pattern. The formulations F1, F2 and F3 contain HPMC-K100 in varying concentration. The higher initial drug release was observed in formulation F1 compared to F2 and F3 respectively. Bilayer tablets of F1, F2, F3 and marketed tablet showed the release of 93.67±2.876, 85.25±0.065, 81.9±2.876 and 99.42±1.328 % at the end of 12 hr respectively. As the concentration of HPMC-K100 increased release of drug in the dissolution medium was decreased. So, varying amount of HPMC-K100 affects the drug release. As expected, the drug release rate was depended on the concentration of the polymer used. The tablet containing optimized concentration of HPMC-K-100 (formulation F3) showed better control of drug release more than 12 hr.

This controlled release of drug from F3 could be attributed to the formulation of the thick gel structure that delays drug release from the Bilayer tablet.

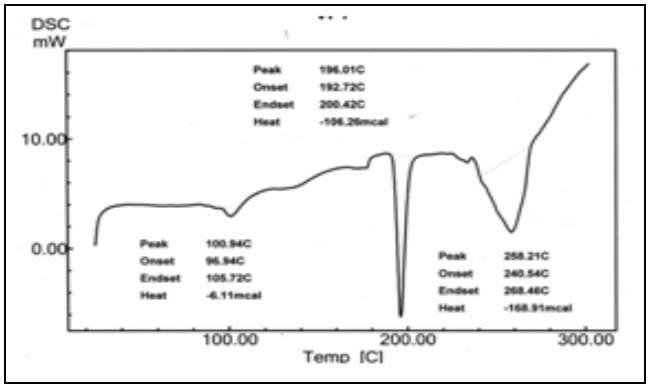

FIG. 4: DSC SPECTRA OF PURE CARBAMAZEPINE

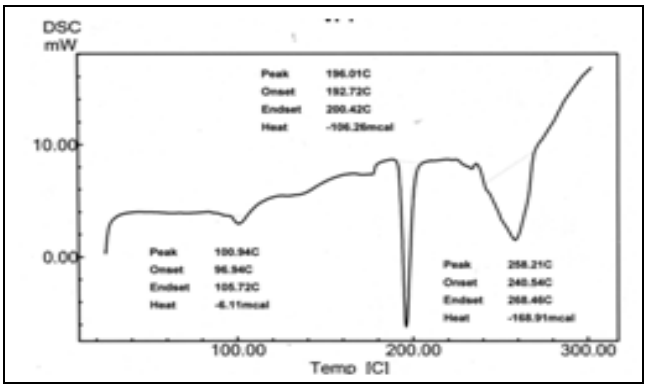

FIG. 5: DSC SPECTRA OF PHYSICAL MIXTURE OF DRUG AND CROSS POVIDONE

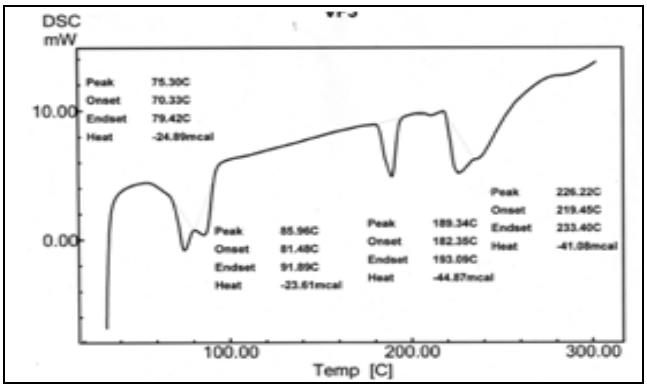

FIG. 6: DSC SPECTRA OF PHYSICAL MIXTURE OF DRUG AND HPMC

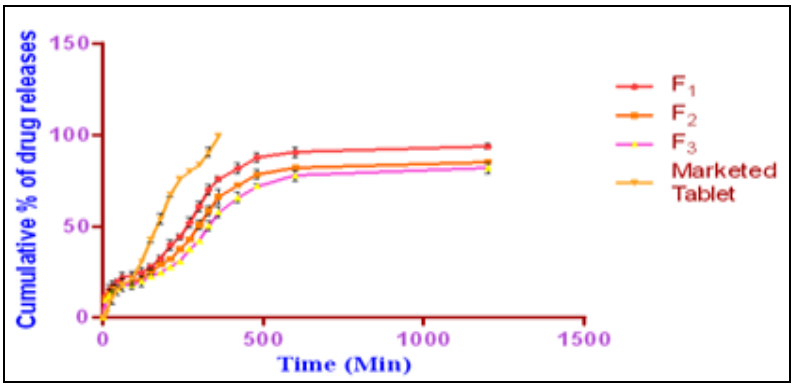

FIG. 7: *IN-VITRO* DISSOLUTION PROFILE OF F1 TO F3 FORMULATION

Kinetic Study:

Drug Release Kinetics: The release kinetics of bilayer layer formulations (F1-F3) was found to following clearly first order kinetics as the values for 'r' is (0.863-0.865). In our experiments, the *in-vitro* release profile from all the formulations could

be best expressed by higuchi's equation as the plot showed high linearity (r^2=0.9186-0.9125). To confirm the mechanism the data was fitted in to Korsmeyer *et al.,* equation all the formulation showed good linearity with slope (n values ranging from 0.6133 to 0.6508) which indicating that analomus diffusion mechanism.

CONCLUSION: Bilayer tablets of CBZ containing immediate release layer and sustained release layer were successfully formulated. All the formulation batches tested for physical parameters like weight variation, hardness, friability and drug content, all were found to be within the pharmacopeial limits. The bilayer tablet showed initial burst release to provide the loading dose of drug followed by sustained release. The formulation F_3 showed better control of drug release more than 12 hr. This controlled release of drug from F_3 could be attributed to the formulation of the thick gel structure that delays drug release from the bilayer tablet. The data obtained thus suggest that bilayer tablet can be successfully designed for sustained delivery of CBZ which is suitable in controlling different types of seizures.

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CONFLICTS OF INTEREST: Nil

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