International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 4(3): May-June 2014

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received: 24-04-2014; Revised; Accepted: 01-05-2014

THE EFFECT OF HYDROXYPROPYLMETHYLCELLULOSE ON THE SUSTAINED RELEASE TABLETS OF CARBAMAZEPINE

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Keywords:

Carbamazepine, carbamazepine dihydrate, floating time, HPMC

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ABSTRACT

Carbamazepine is a widely used anti-epileptic drug in the therapy of psychomotor seizures and trigeminal neuralgia. The main objective of the present investigation is to develop cost effective and easy method for the formulation of tablets and to study effect of hydroxypropylmethylcellulose on the in-vitro release of CBZ tablet and to study change in the CBZ forms by recrystallisation. Floating tablets where prepared using direct compression method.The tablets were evaluated for preformulation studies like angle of repose, bulk density, and physical characteristics like ,thickness, diameter, drug content, floating lag time, floating time, *in vitro* dissolution study. The anhydrous carbamazepine gets converted into dihydrate form and show different release pattern. Dihydrate form of the carbamazepine fallowed zero order which is independent of concentration of drug present. The hydroxypropylmethylcellulose used in formulation found to inhibit the formation of dihydrate. The release of the best batch with both HPMC K4M and HPMC K100M showed 12 hrs extended release which is found to be effective for the treatment of epilepsy.

INTRODUCTION

Carbamazepine (CBZ) is the drug widely used as the anti-epileptic in the therapy of psychomotor seizures and trigeminal neuralgia. The popularity of this drug is related to beneficial properties including poor efficacy in controlling different type of seizures. Sustained release formulation of carbamazepine is capable of maintaining the patient's blood concentration to therapeutic level for atleast 12 hr period. To achieve the therapeutic level the drug should be formulated in the dosage form that will reliably remain in GI tract and favor absorption in the blood for 12 hrs. Thus gastroretentive drug delivery system for CBZ is proposed.[1]Patel D et al formulated the gastroretentive CBZ tablets using bees-wax, melting granulation.

Anhydrous form of CBZ get converted into CBZ dihydrate . Hydroxypropylcellulose inhibit the formation of CBZ dihydrate. Hydroxy propylmethyl cellulose (HPMC) hydrophilic matrix system should possess a polymer that will wet, hydrate and swell to form a gelatinous layer and avoid disintegration of the tablet and is most widely studied hydrophilic swellable matrix forming material for the preparation of modified drug release products. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release,ease of compression, and its capability to accommodate high levels of drug loading.[2]

The main objective of the present investigation is to develop cost effective and easy method for the formulation of tablets and to study effect of hydroxypropylmethylcellulose on the in-vitro release of CBZ tablet and to study change in the CBZ forms by recrystallisation.

MATERIALS

Carbamazepine was received as a gift sample by Amoli Organics Pvt Ltd. Hydroxlpropyl methylcellulose K4M and hydroxypropylmethylcellulose K100M were obtained as gift sample from Colorcon Pvt Ltd. Sodium bicarbonate, lactose monohydrate, sodium lauryl sulphate(SLS), talc magnesium stearate , Hcl, ethanol and methanol were obtained from S.D Fine chemicals. Other solvents procured were of analytical grade obtained from Merck specialities pvt ltd.

METHODS

Tablets were prepared by direct compression method using lactose monohydrate as diluents and hydrophilic polymers such as HPMC K4M and HPMC K100M. All the powders where passed through the sieve no-16. The sieved powder with the drug was then compressed on 12mm single punch tablet machine. The tablets were white and round. Nine formulation was prepared and coded them F_1-F_9. The detail of composition is given in the table.

PREPARATION OF CARBAMAZEPINE DIHYDRATE.[8,9,10]

Drug polymorphs were formed by recrystallisation. Carbamazepine in four sets were dissolved in ethanol at 65°C, the obtained solution was treated under different conditions such as

- The Solution was directly transferred to freezer.
- The solution after reaching room temperature, stored in freezer.
- The solution was kept at room temperature.

The solution was directly added to ice cold water and then stored at room temperature.

COMPATIBILITY STUDIES

Physical mixture of anhydrous CBZ and polymer and only carbamazepine dehydrate were mixed with IR grade potassium bromide (KBr) and prepared transparent pellets.[2]

EVALUATION OF FORMULATION BLEND

The flow properties of the formulation blend where characterized in term of angle of repose, tapped density, bulk density and carr's index and hausner's ratio.

It is expressed in percentage and is expressed by eq.1

$$I = Dt - Db / Dt \ldots\ldots\ldots\ldots (1)$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner ratio

It is expressed in percentage and is expressed by eq.2

$$H= Dt / Db \ldots\ldots\ldots (2)$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.[4]

DRUG CONTENT ESTIMATION OF TABLETS.[11]

Drug content was estimated by using HPLC system.

Column: Purospher® STAR LP RP 18e 150× 4.6×5µm

Injection: 10 µl

Detection: Shimadzu prominence UV 285nm

Cell :

Flow rate : 1.00ml/min

Mobile phase : Take 500ml distill water in a beaker. Adjust ph 2.5 with orthophospheric acid and ACN in ratio 70:30

Temperature : 25^0c

Diluent : Water: ACN (50:50)

Pressure : 96 bar (1392 psi)

Standard : weigh 5mg of carbamazepine std. Transfer it in 50ml volumetric flask. Dissolve it and make up volume up to mark with diluent.

Sample : Crush 10 tablets and weigh the blend equivalent to 5mg of carbamazepine. Transfer it in 50ml volumetric flask. Dissolve it in diluents and sonicate it for 15 mins. Make up the volume up to the mark, filter through 4.45 µm membrane.

***IN-VITRO* DISSOLUTION STUDIES**

The release rate of Carbamazepine and carbamazepine dihydrate from matrix tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle apparatus). The dissolution test was performed using 900 ml of gastric simulated fluid, at 37 ± 0.5°C , 75 rpm for 12 hours. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 30 min, 1hr,3h, 6hr, 9hr, 12 hr and the samples were replaced with fresh dissolution medium. Absorbance of these solutions was measured at 285 nm using a UV/Visible spectrophotometer. The percentage drug release was plotted against time to determine the release profile.[2]

EVALUATION PARAMETERS FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

Floating lag time – Tablet was placed in 500 ml beaker containing 400ml gastric simulated fluid pH 1.2. then the time taken by the tablet to move from bottom to top of the beaker was measured.[7]

Duration of buoyancy- Duration of buoyancy was observed simultaneously during the measurement of floating lag time. The time taken by the tablet to rise on the surface of the medium i.e gastric simulated fluid pH 1.2 and the time taken by the tablet to sink at the bottom was taken into consideration and the difference of the both gives the duration of buoyancy.[7]

Floating time- Floating lag time was observed at the same time during measurement of floating lag time and duration of buoyancy. The time for which the tablet moves on the surface of the medium was measured.[7]

% water uptake- The swelling properties of HPMC matrices containing drug was determined by placing tablet in the beaker containing gastric simulated fluid pH 1.2. the tablet was removed periodically from the dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling index was expressed in terms of water uptake .[12]

% water uptake = weight gain of swollen tablet- initial weight of tablet/ initial weight of tablet.

RESULTS AND DISCUSSION

Used polymer was compatible with drug as seen in fig- 1,2,3. Carbamazepine when exposed to moisture get converted into carbamazepine dihydrate and no sharp peak is seen at 3460 cm^{-1} in IR of carbamazepine as seen in fig-4, whereas no sharp peak is seen in case of carbamazepine anhydrous. The HPMC polymer used inhibit the formtion of carbamazepine dihydrate as seen in fig 2,3.Formulation blend of all batches shown the excellent release. Floating time of the best batches F6 was found to be 24 hrs whereas floating lag time was 6 secs as shown in the table 6. Dissolution studies where carried out and the best batch F6 showed first order release kinectics. i.e release depend upon the concentration of the drug present thus therapeutic level is maintained in case of the drug used that is carbamazepine. It was also seen that if HPMC K4M used alone the release was found to be Immediate whereas HPMC K100M release was extended but was found to be very slow. So it was concluded that the combination of both polymer show proper release. Swelling index was about 78%. The % content of drug in floating tablets was found to be 100%.

CONCLUSION

The F6 formulation with combination of HPMC K4M and HPMCK100M followed the first order release kinectics and higuchi release mechanism, i.e the drug release was with the diffusion.The floating lag time was found to be 26 secs and thus the duration of buoyancy was found to be less. The floating time was 24 hrs, in which 12 hrs release and matrix was found to be floating after the complete release of the drug.

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Table 1- COMPOSITION OF BLEND IN TABLET

(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Drug	200	200	200	200	200	200	200	200
Sodium bicarbonate(10%)	50	50	50	50	50	50	50	50
Citric acid	-	-	10	10	-	-	-	10
SLS (1%)	-	-	-	-	5	-	5	-
HPMC K4M	75	-	80	-	63.7	63.7	56.2	56.2
HPMC K100M	-	75	-	80	11.2	11.2	18.7	18.7
Carbopol	-	-	20	20	-	-	-	-
Mg stearate	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Lactose	162	162	135	137	162	167	162	167

Table 2- EVALUATION OF FORMULATION BLEND OF TABLETS

Batches	Tap density (g/cm^3)	Bulk density (g/cm^3)	Carr's index (I_c)	Hausner's ratio H_r	Angle of repose
1	0.827	0.791	1.044	4.29	18.127
2	0.820	0.794	1.03	3.170	17.92
3	0.732	0.689	1.06	5.87	18.12
4	0.731	0.688	1.06	5.88	18.12
5	0.764	0.714	1.070	6.54	27.36
6	0.765	0.713	1.072	6.79	27.36
7	0.712	0.663	1.073	6.88	26.56
8	0.767	0.714	1.073	6.91	26.56

Table 3- RELEASE KINETICS OF FORMULATION

Batch	Zero order		First order		Release order
	Equation	R^2	Equation	R^2	
F1	Y=6.067x+14.51	0.991	Y=0.061x+1.270	0.926	Zero
F2	Y=4.756x+4.393	0.866	Y=0.067x+1.007	0.962	First
F3	Y=3.843x+90.23	0.861	Y=0.015x+1.955	0.812	Zero
F4	Y=4.041x+38.55	0.929	Y=0.030x+1.597	0.863	Zero
F5	Y=7.156x+25.330	0.974	Y=0.049x+1.472	0.996	First
F6	Y=5.202x+24.82	0.940	Y=0.041x+1.462	0.987	First
F7	Y=6.335x+18.95	0.971	Y=0.053x+1.384	0.969	Zero
F8	Y=5.523x+32.58	0.993	Y=0.038x+1.5550	0.979	Zero
M	Y =3.978x+33.77	0.862	Y=0.034x+1.527	0.778	Zero
C1	Y =6.398x+24.15	0.996	Y = 0.052x +1.429	0.833	Zero
C2	Y =5.348x+34.34	0.956	Y=0.039x+1.557	0.867	Zero
C3	Y= 4.589 + 22.10	0.991	Y=0.043+1.398	0.969	Zero

Table -4 RELEASE MECHANISM OF FORMULATION

Batches	Higuchi		Hixoncrowell		Korsmeyer-peppas		Release mechanism
	Equation	R^2	Equation	R^2	Equation	R^2	
F1	y=25.13x-5.197	0.970	Y=-0.072x+5.719	0.989	Y=0.529x+1.328	0.987	Hixson-crowell
F2	Y=18.69x-9.082	0.764	Y=0.054x+5.818	0.842	Y=0.678x+0.957	0.788	Hixson-crowell
F3	Y=0.053+1.937	0.972	Y=-0.063+4.787	0.896	Y=0.123x+1.981	0.989	
F4	Y=0.106x+1.555	0.941	y=-0.050+5.449	0.941	Y=0.233x+1.649	0.873	
F5	Y=29.20x+2.055	0.904	Y=-0.096+5.612	0.950	Y=0.398x+1.541	0.896	Hixson- crowell
F6	Y=0.174x+1.315	0.932	Y=-0.065x=5.612	0.917	Y=0.376x+1.475	0.829	Higuchi
F7	Y=0.224x+1.207	0.987	Y=-0.082+5.680	0.948	Y=0.499x+1.401	0.938	Hixson crowell
F8	Y=0.160x+1.429	0.990	Y=-0.071x+5.529	0.985	Y=0.355x+1.57	0.930	higuchi
M	Y=0.125+1.473	0.894	Y=-0.297x+1.57	0.885	Y=0.297+1.57	0.966	Korsmeyer-peppas
C1	Y=0.199x+1.135	0.976	Y=-0.083x+5.531	0.972	Y=0.454x+1.480	0.975	Higuchi
C2	Y=0.137x+1.504	0.977	Y=-0.066x+5.553	0.969	Y=0.302x+1.623	0.918	Higuchi
C4	Y=0.177x+1.26	0.985	Y=-0.053x+5.681	0.988	Y=0.391+1.420	0.924	Hixson crowell

Table -5 DIAMETER AND THICKNESS OF TABLETS FORMULATED

Batches	Diameter	Thickness
F1	10.28± 0.0282	1.32± 0.11313
F2	10.3± 0.00	1.45± 0.0707
F3	10.33± 0.0424	1.44± 0.2262
F4	10.4± 0.00	1.59± 0.07071
F5	10.36± 0.1414	1.45± 0.21213
F6	10.36± 0.1414	1.45± 0.21213
F7	10.33± 0.0989	1.2± 0.0565
F8	10.33± 0.0989	1.2± 0.0565

Table-6 EVALUATION OF FLOATING PARAMETERS OF FORMULATED BATCH

Batches	Floating lag time (secs)	Floating time (hrs)
F1	9.3 ± 0.577	18
F2	29.33±0.577	48
F3	16 ± 3.6051	24
F4	9.33 ± 2.081	24
F5	25.76±0.5196	24
F6	25.76 ± 0.2098	24
F7	40.166 ± 0.057	24
F8	30.76 ± 1.2112	24

Table -7 CHROMATOGRAPHIC PARAMETERS OBTAINED DURING ASSAY OF FORMULATED TABLET

Sample	Retention time	Area
Standard	10.660	6527853
Sample	10.734	6115987

Figure 1 IR OF CBZ

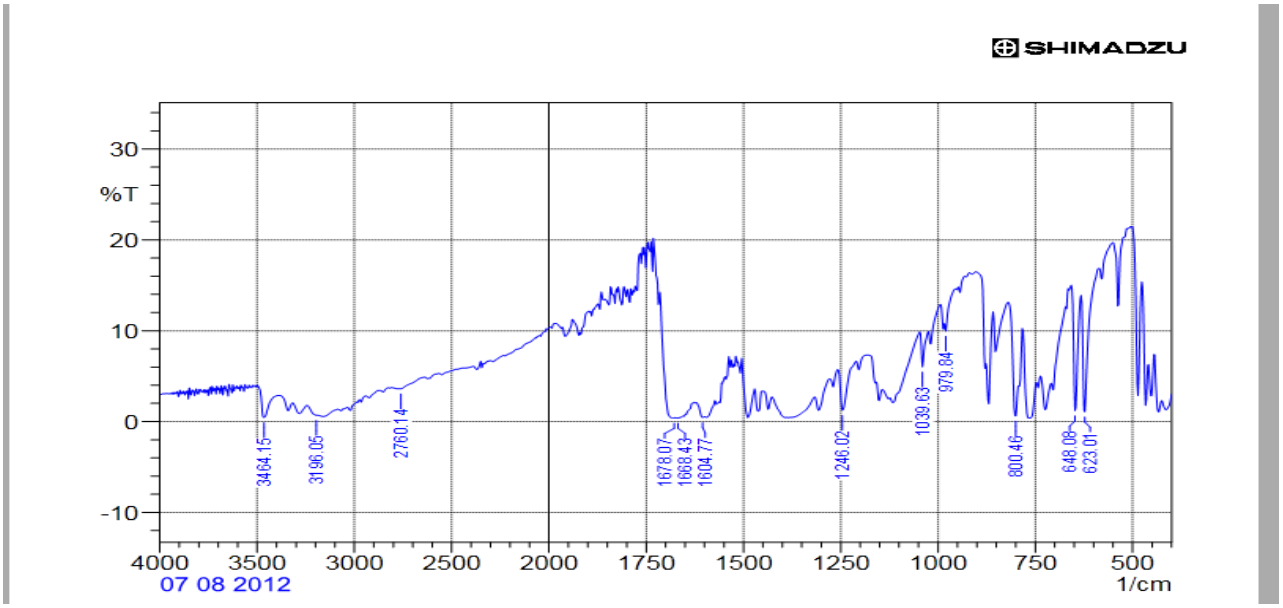

Fig-2 IR OF CBZ + HPMC K4M

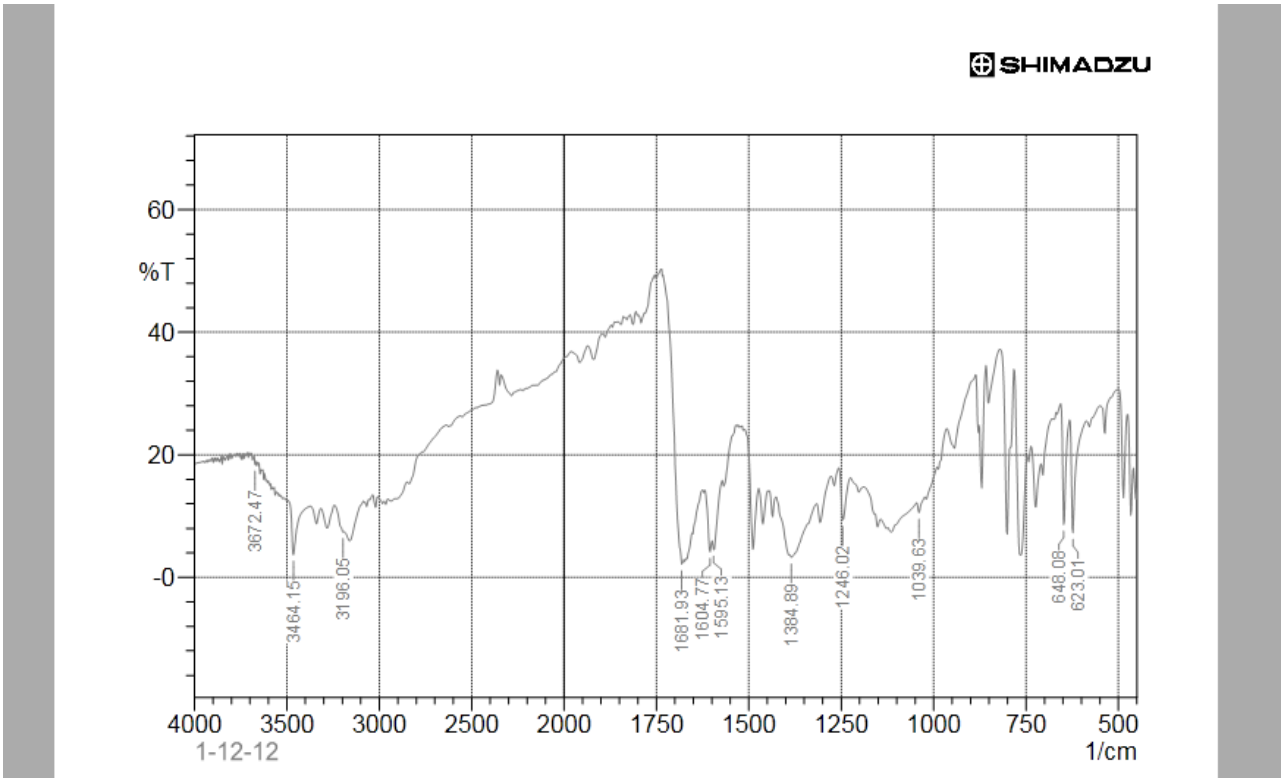

Fig-3 IR OF CBZ +HPMCK100M

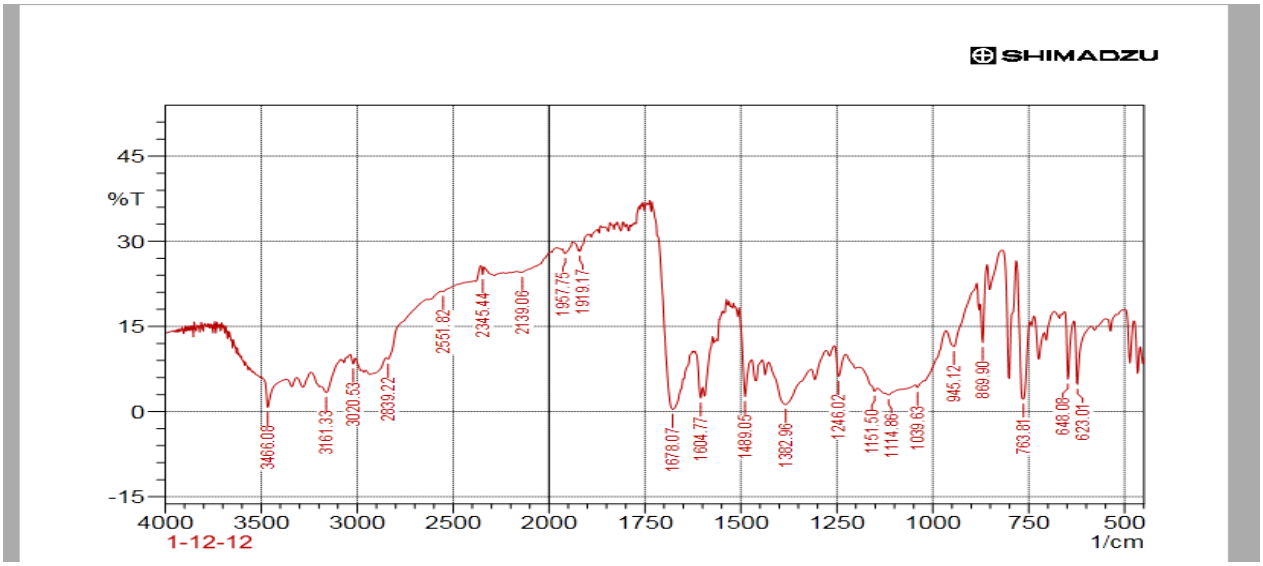

Fig -4 IR OB CBZ DIHYDRATE

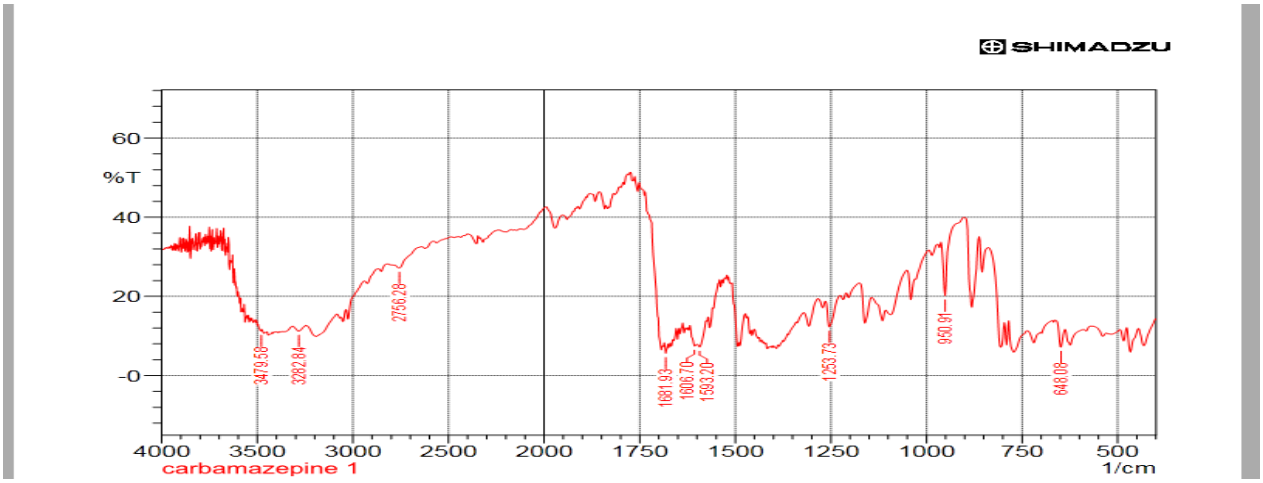

Fig -5 CALIBRATION CURVE OF THE DRUG

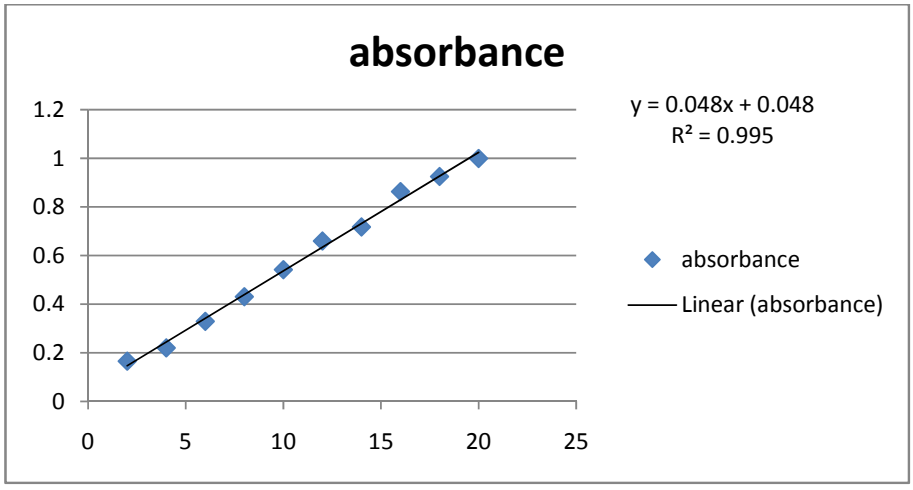

Fig -6 DISSOLUTION GRAPH OF ALL BATCHES.- CBZ ANHYDROUS FORM.

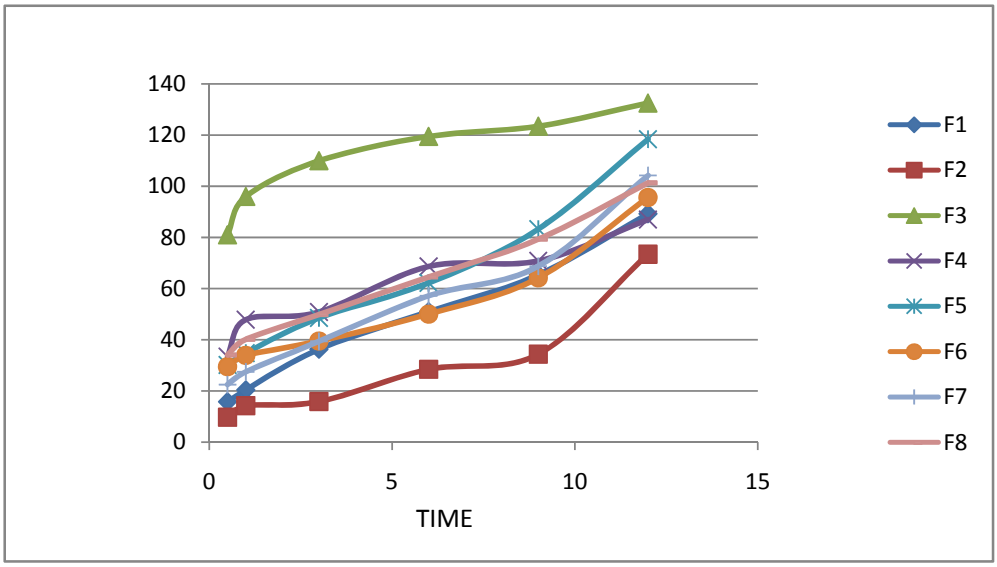

Fig 7 DISSOLUTION GRAPH –COMPARISION OF F6 WITH CBZ DIHYDRATE FORMULATION

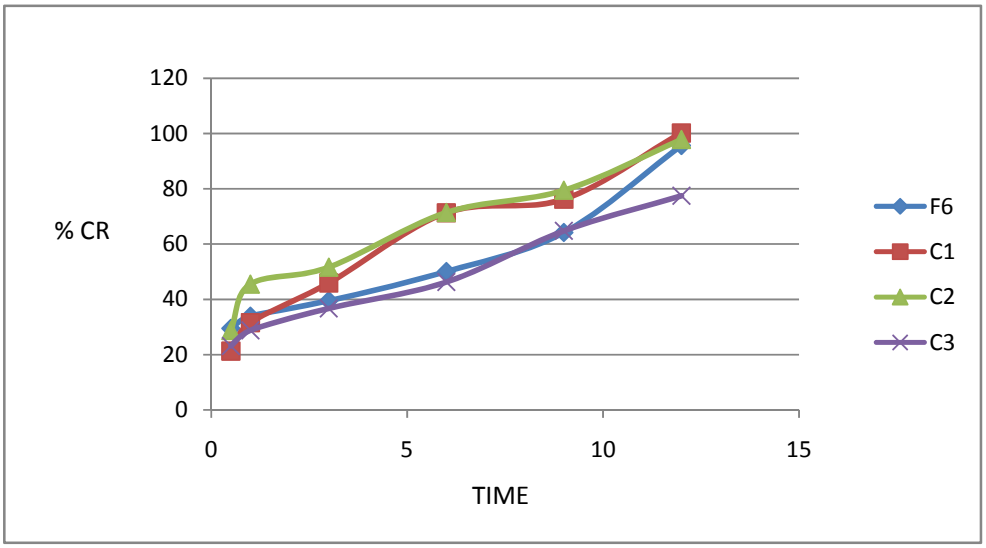

Fig -8 CHROMATOGRAM- CBZ STD OBTAINED BY FOLLOWED BY ABOVE DRUG CONTENT PROCEDURE

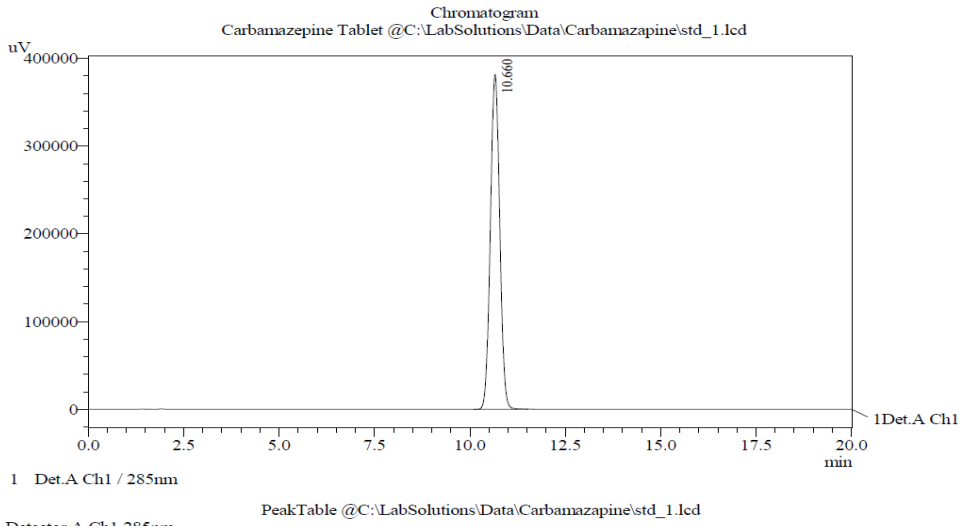

Fig -9 CHROMATOGRAM CBZ SAMPLE OBTAINED BY FOLLOWED BY ABOVE DRUG CONTENT PROCEDURE