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Research

Formulation Development And *In Vitro* Characterization Of Carbamazepine Extended Release Matrix Tablets

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Abstract

The present study was aimed to developed formulation of extended release (ER) tablets of Carbamazepine using HPMC K100M, Carbopol 71 G, and HPMC (K4M) polymer. Carbamazepine extended release tablets were prepared by direct compression method by employing polymer (HPMC K100M, Carbopol 71 G, HPMC (K4M) and Eudragit RSPO). The matrix granules were prepared by mixing drug along with polymer and diluents in different polymer ratio. The prepared granules were evaluated for various physicochemical parameters by official procedure and compressed in tablets. *In-vitro* release profiles of Carbamazepine from extended release tablets were determined using USP apparatus type II (Paddle), 50rpm and bath temperature 37ºC. Tablets dissolution was carried out in 900 ml of media (0.1N HCL and 6.8 phosphate buffer). Samples were withdrawn at predetermined time intervals up to 24 Hrs and analyzed using UV at a wavelength of 225 nm. It followed First order release kinetics mechanism.

Keywords: Carbamazepine, HPMC K100M, Carbopol 71 G, HPMC (K4M), Eudragit RSPO and extended release tablets.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. [1,2]

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drugdelivery system, two pre-requisites would be required: Firstly single

dose for the duration of treatment whether for days or weeks as with infection, diabetes orhypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.[3]

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the caregiver as well.[4]

Drawbacks of Conventional Dosage Form[5]

- ✓ Poor patient compliance, increased chances of missing the dose of a drug with short halflife for which frequent administration is necessary.
- ✓ The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- ✓ A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- ✓ The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Advantages of Extended Release Delivery System[6]

- ✓ The extended release formulations reduce dosing frequency of drugs.
- ✓ The extended release formulations may maintain therapeutic concentrations.
- ✓ Reduce the toxicity by slowing drug absorption.
- ✓ The use of these formulations avoids the high blood concentration.
- ✓ Extended release formulations have the potential to improve the patient compliance and convenience.
- ✓ Minimize the local and systemic side effects.
- ✓ Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- ✓ Improvement in treatment efficacy.
- ✓ Minimize drug accumulation with chronic dosing.
- ✓ Improve the bioavailability of some drugs.
- ✓ Usage of less total drug.
- ✓ Improve the ability to provide special effects. For example, Morning relief of arthritis through bed time dosing.

Disadvantages of Extended Release Delivery System[6]

- ✓ Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- ✓ The larger size of extended release products may cause difficulties in ingestion or transit through gut.
- ✓ The release rates are affected by various factors such as food and the rate of transit through the gut.
- ✓ Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- ✓ High cost of preparation.
- ✓ Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

Rationale of Extended Drug Delivery[7]

The main objective to formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favourable. This change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameters.

Pellets

Pelletization is an agglomeration process, that converts fine powder blend of drug(s) and excipients into small, free flowing, spherical units, referred to as pellets. Rationale of extended release pellets Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and can also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.

Advantages of extended release pellets

- ✓ Reduce dosing frequency of drugs.
- ✓ Maintain therapeutic concentrations.
- ✓ Reduce the toxicity by slowing drug absorption.
- ✓ The use of pellets avoids the high blood concentration.
- ✓ Extended release formulations have the potential to improve the patient compliance and convenience.
- ✓ Minimize the local and systemic side effects.
- ✓ Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- ✓ Improvement in treatment efficacy.
- ✓ Minimize drug accumulation with chronic dosing.
- ✓ Improve the bioavailability of some drugs.
- ✓ Usage of less total drug.
- ✓ Improve the ability to provide special effects.[8]

Drugs those are Unsuitable for Such Design

- ✓ Elimination half-life less than 2 hours. ·
- ✓ Administered in large dose. ·
- ✓ Therapeutics index is narrow. ·
- ✓ Poor water solubility. ·
- ✓ Long elimination half-life.
- ✓ Drugs having extensive first-pass clearance.[9,10,11,12]

Approaches to Achieve Extended Release Matrix Tablet

The purpose of designing ER dosage form is to develop a reliable formulation that has all the advantages of immediate release dosage form and yet devoid of the dose dumping. The fundamental principle in design of extended release tablet are to slowing down of absorption, bio transformation and excretion rate respectively. Various techniques have been used in the formulation of ER products. In general, extended formulations can be divided into different categories based on the mechanism of drug release.

1) Diffusion controlled release system.
2) Dissolution controlled release system.
3) Ion exchange resin drug complex.
4) Swelling controlled release

MATERIALS AND METHODS

Carbamazepine-Provided by SURA LABS, Dilsukhnagar, and Hyderabad, HPMC K100M- Degussa India Ltd. (Mumbai, India), Carbopol 71-G Laser Chemicals, Ahmadabad, India, HPMC (K4M) Merck Specialities Pvt Ltd, Mumbai, India, Eudragit RSPO-Merck Specialities Pvt Ltd, Mumbai, India, PVP K 30-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium Stearate-Merck Specialities Pvt Ltd, Mumbai, India, MCC ph102-Merck Specialities Pvt Ltd, Mumbai, India.

Methodology

Analytical method development

Determination of Wavelength

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution–100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Table 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$\text{Bulk Density} = M / V_o$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$\text{Tap} = M / V$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Carbamazepine. Total weight of the tablet was considered as 500mg.

Procedure

1) Carbamazepine and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 3: Formulation composition for tablets

Ingredients (MG)	Formulation								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carbamazepine	100	100	100	100	100	100	100	100	100
HPMC K100M	40	80	120	-	-	-	-	-	-
Carbopol 71 G	-	-	-	40	80	120	-	-	-
HPMC (K4M)	-	-	-	-	-	-	40	80	120
Eudragit RSPO	100	100	100	100	100	100	100	100	100
PVP K 30	40	40	40	40	40	40	40	40	40
Talc	10	10	10	10	10	10	10	10	10
Magnesium Stearate	12	12	12	12	12	12	12	12	12
MCCph102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	500	500	500	500	500	500	500	500	500

All the quantities were in mg

RESULT AND DISCUSSION

The present study was aimed to developing extended release tablets of Carbamazepine using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method

Graphs of Carbamazepine were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 285 nm and 288 nm respectively.

Table 4: Observations for graph of Carbamazepine in 0.1N HCl (285nm)

Conc. [µg/ml]	Absorbance
0	0
2	0.126
4	0.231
6	0.342
8	0.452
10	0.571

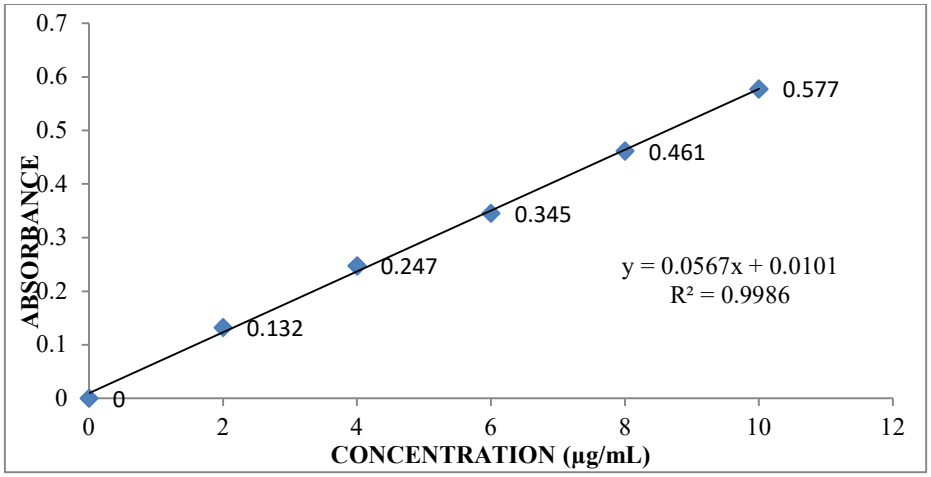

Fig 1: Standard graph of Carbamazepine in 0.1N HCl

Table 5: Observations for graph of Carbamazepine in pH 6.8 phosphate buffer (288nm)

Concentration [µg/ml]	Absorbance
0	0
2	0.132
4	0.247
6	0.345
8	0.461
10	0.577

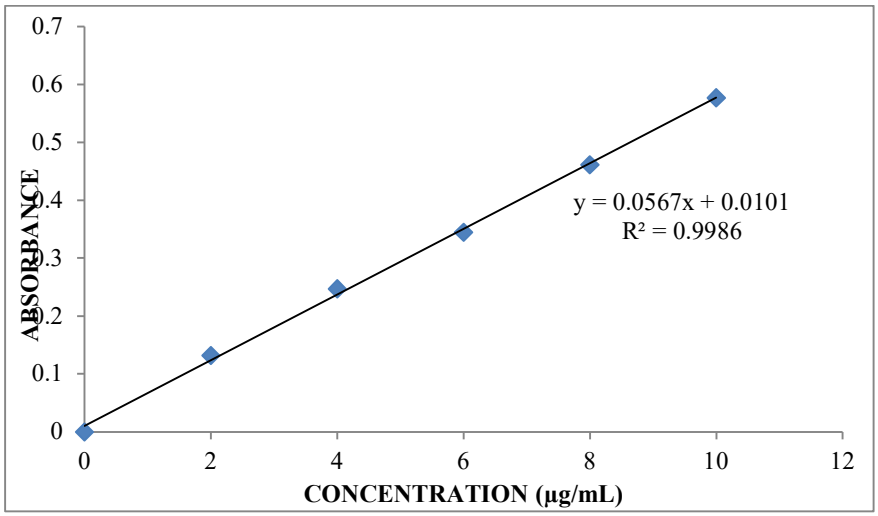

Fig 2: Standard graph of Carbamazepine pH 6.8 phosphate buffer (288nm)

Preformulation parameters of powder blend

Table 6: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	28.23	0.47	0.55	14.54	1.17
F2	27.91	0.45	0.55	18.18	1.22
F3	26.71	0.46	0.55	16.36	1.19
F4	26.71	0.46	0.55	16.36	1.19
F5	28.23	0.47	0.55	14.54	1.17
F6	29.34	0.50	0.58	13.79	1.16
F7	26.78	0.41	0.50	18	1.21
F8	29.34	0.50	0.58	13.79	1.16
F9	26.78	0.41	0.50	18	1.21

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41 to 0.50 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50 to 0.58 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.22 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

***In-vitro* quality control parameters for tablets**

Table 7: *In-vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	498.56	5.3	0.35	5.26	98.31
F2	499.21	5.0	0.42	5.15	99.34
F3	500.01	4.9	0.65	5.36	96.24
F4	497.59	5.2	0.41	5.14	99.10
F5	498.35	4.6	0.39	5.22	100.03
F6	499.78	5.0	0.55	5.82	97.42
F7	500.00	5.4	0.61	5.60	98.36
F8	498.79	5.5	0.59	5.13	99.25
F9	499.26	4.8	0.47	5.48	97.14

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 497.59 to 500.01 mg, so the permissible limit is ±7.5% (>500mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 5.5 to 4.9 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 5.13 to 5.82 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 96.24 -100.03 %. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-vitro* drug release studies**

Table 8: Dissolution data of Carbamazepine tablets

TIME	CUMULATIVE PERCENT DRUG DISSOLVED								
(H)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	7.61	5.35	4.95	9.14	7.52	06.52	6.25	4.31	3.62
4	27.26	24.83	21.31	41.60	35.43	22.91	21.12	20.52	18.75
8	47.96	41.61	36.67	56.56	38.97	35.82	40.56	36.98	32.98
12	73.57	71.15	67.52	76.13	68.69	65.94	71.35	68.36	62.76
16	84.34	80.75	78.74	89.75	76.28	74.56	80.92	78.61	70.12
24	97.21	94.56	90.61	98.82	90.15	89.71	90.84	87.18	86.34

Formulations prepared with HPMC K100M retarded the drug release in the concentration of 40 mg (F1 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.21 % in 24 hours with good retardation. From the dissolution data it was evident that the formulations prepared with different concentrations as 40, 80 and 120mg polymer were retard the drug release up to desired time period i.e., 24 hours. Where as in case of formulations prepared with different concentrations as 40, 80 and 120mg retarding polymer, the formulations with 40 mg concentration of polymer showed complete drug release in 24 hours only, The Formulation Containing concentration in 40 mg of Carbopol 71 G Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.82%. From the above results it was evident that the formulation F4 is best formulation with desired drug release pattern extended up to 24 hours.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 9: Release kinetics data for optimised formulation

Cumulative (%) Release Q	Time (T)	Root (T)	Log(%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
9.14	2	1.414	0.961	0.301	1.958	4.570	0.1094	-1.039	90.86	4.642	4.496	0.146
41.6	4	2.000	1.619	0.602	1.766	10.400	0.0240	-0.381	58.4	4.642	3.880	0.762
56.56	8	2.828	1.753	0.903	1.638	7.070	0.0177	-0.247	43.44	4.642	3.515	1.126
76.13	12	3.464	1.882	1.079	1.378	6.344	0.0131	-0.118	23.87	4.642	2.879	1.762
89.75	16	4.000	1.953	1.204	1.011	5.609	0.0111	-0.047	10.25	4.642	2.172	2.469
98.82	24	4.899	1.995	1.380	0.072	4.118	0.0101	-0.005	1.18	4.642	1.057	3.585

Drug – Excipient compatibility studies
Fourier Transform-Infrared Spectroscopy

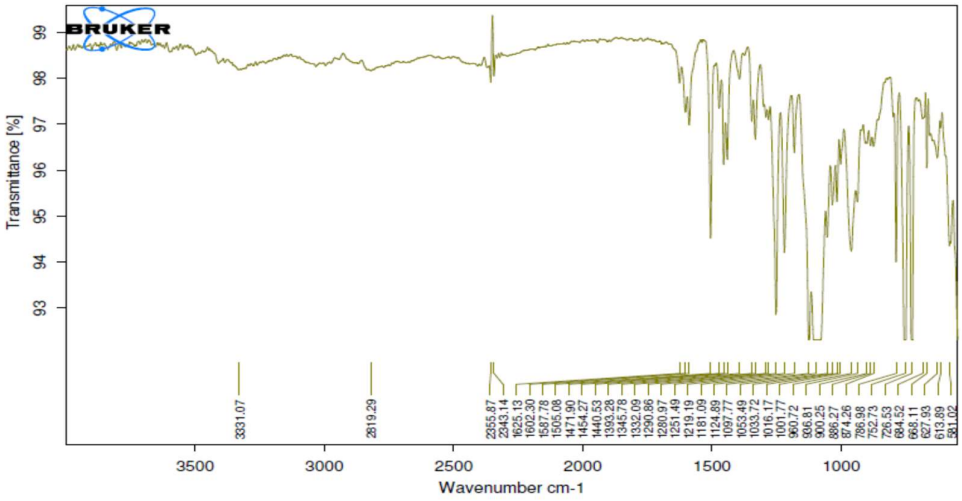

Fig 3: FT-IR Spectrum of pure drug

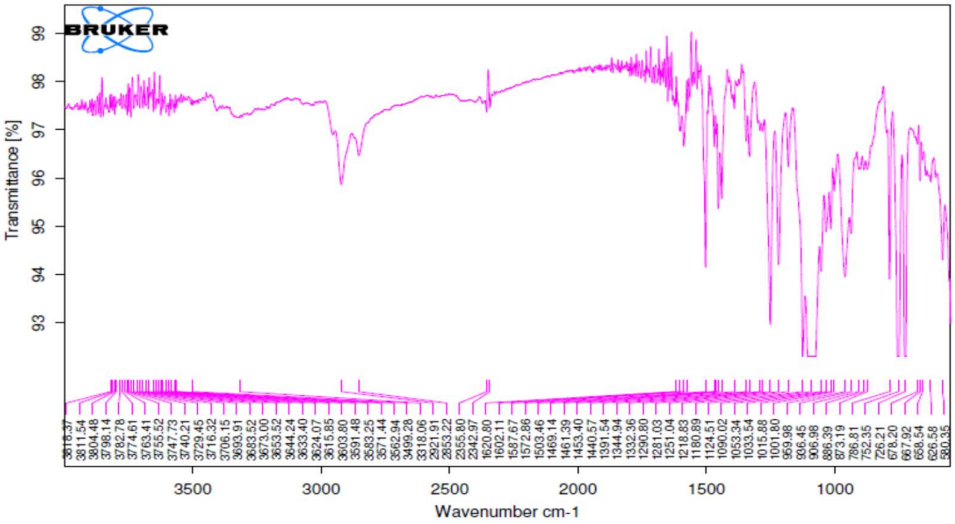

Fig 4: FT-IR Spectrum of Optimized Formulation

CONCLUSION

Carbamazepine is a medication used to treat epilepsy and neuropathic pain. It is also used to treat adults with heart failure and chronic kidney disease.The present study was aimed to develop extended release tablets of Carbamazepine using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies. Extended release tablets of Carbamazepine is to be prepared by direct compression technique using various polymers, namely HPMC K100M, Carbopol 71 G, HPMC (K4M) and Eudragit RSPO. The FTIR spectra of Carbamazepine and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible. Tablet powder blend was subjected to various pre-formulation parameters and Post formulation parameters were found to be within limits. From the dissolution results it was evident that the formulation F4 is best formulation with desired drug release pattern extended up to 12 hours 98.82%.Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and

Korsmeyer-Peppas release model and it was evident that the formulation F4 was followed First order release kinetics.

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