IJBPAS, July, 2026, 15(7): 3034-3045

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION AND EVALUATION OF OXCARBAZEPINE EXTENDED-RELEASE TABLETS BY USING CO-CRYSTAL METHOD

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Received 14th June 2025; Revised 20th July 2025; Accepted 18th Aug. 2025; Available online 1st July 2026

https://doi.org/10.31032/IJBPAS/2026/15.7.10239

ABSTRACT

In the present investigation an attempt has been made to enhance the solubility and dissolution rate, thereby increasing bioavailability and improved patient compliance by developing extended-release tablets of Oxcarbazepine. Oxcarbazepine co-crystals were prepared with co-formers like benzoic acid, tartaric acid and oxalic acid. The efficient co-crystals were further directly compressed to extended-release tablets with various rate controlling polymers like chitosan, HPMC K10M, Carbopol 940. The prepared tablets were evaluated for Pre compression and Post compression studies and results were found to be within acceptable limits. The drug excipient compatibility studies were confirmed by FTIR and DSC. The *In-vitro* dissolution studies were performed for the prepared tablets and observed that formulation containing 8% chitosan shows the release of the drug about 82.4% for 8 hrs and it follows zero-order release mechanism with non-fickian super case-II transport. The developedformulation shows 63% similarity with marketed product. Stability studies wereconducted for formulation (F2) at 40ºC ± 5% RH for a period of 1 month and results were found to be within the limits. Hence the formulation F2 wasconsidered as best formulation.

Key words: Oxcarbazepine, co-crystals, extended-release tablets, direct compression, rate controlling polymers

INTRODUCTION

Solubility and dissolution rates are important factors in determining the efficacy and activity of a drug. Early drug discovery studies were based on traditional remedies or serendipitous discoveries. Many new drug targets have been identified and potential drug molecules have been synthesized and analyzed for efficacy, employing advanced techniques such as high-throughput screening and combinatorial chemistry. The lead molecules discovered utilizing these screens are increasingly large and lipophilic in nature. Therefore, the need of today's era is to decrease problems regarding the solubility and permeability of lipophilic drugs by using different methods. Various approaches have been described by the researchers to enhance the solubility of APIs such as by formation of prodrugs, solid dispersions, size reduction, inclusion complexes with cyclodextrins, salt formation, self-emulsifying formulations, the use of surfactants, polymorphs, nanoparticles and the use of multicomponent molecular crystals. All the above techniques have their own merits and demerits but rate of success will always depend on the specific physicochemical properties of the APIs and polymers.

Mechanism involved in the solubility of co-crystals:

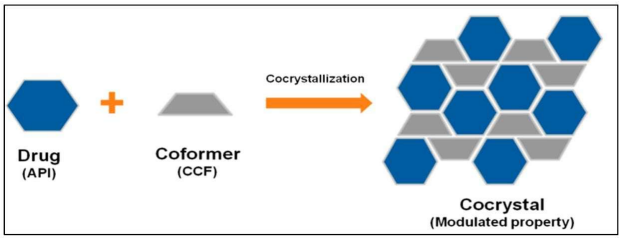


Figure 1: Mechanism involved in the solubility of co-crystals

The solubility is majorly dependent on two factors in co-crystals i.e. strength of crystal lattice and the salvation of co-crystals. One can enhance solubility by reducing the lattice energy and/or enhancing the solvent affinity. The co-crystals have the capability to influence both factors to different extent.

Methods of preparation of co-crystals:

Different techniques are used for the preparation of co-crystals they are as follows:

Traditional Techniques:

1. Solvent evaporation technique
2. Solid state grinding or mechanical milling technique
3. Solvent reduced technique
4. Slurrying technique
5. Solvent drop technology

Advanced Techniques:

1. Microwave assisted synthesis
2. Super critical fluid technology
3. Ultrasound assisted solution co-crystallization
4. Spray Drying
5. High Shear Granulation

MATERIALS AND METHODS

Table 1:

S. No.	MATERIAL	MANUFACTURER
1.	Oxcarbazepine	Hetero Laboratories
2.	Benzoic acid	Thermo Electron, Pvt. Ltd
3.	Tartaric acid	Molychem Pvt. Ltd
4.	Oxalic acid	Thermo Fischer Pvt. Ltd
5.	Acetone	Merk life sciences Pvt. Ltd
6.	Methanol	Fischer scientific Pvt. Ltd
7.	Chitosan	Ozone internationals, Mumbai
8.	HPMC K10	Ozone internationals, Mumbai
9.	Carbopol 940	Ozone internationals, Mumbai
10.	Microcrystalline cellulose	Kemphasol (Mumbai, India)
11.	Magnesium stearate	Ozone internationals, Mumbai
12.	Talc	Kemphasol (Mumbai, India)

Formulation of Co-Crystals:

Table 2: Formulation of Co-Crystals:

Formulation	Oxcarbazepine	Oxalic acid	Tartaric acid	Benzoic acid
F1 (1:1)	150	150	-	-
F2 (1:2)	150	300	-	-
F3 (1:1)	150	-	150	-
F4 (1:2)	150	-	300	-
F5 (1:1)	150	-		150
F6 (1:2)	150	-		300

Preparation of Co-Crystals:

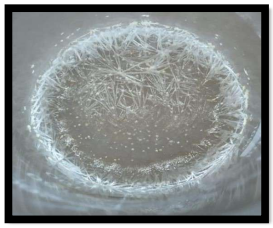
Co-Crystals of Oxcarbazepine were prepared by solvent evaporation method.

Solvent Evaporation Method:

Drug and co-former dissolved in 50ml acetone by stirring. It is stirred continuously until clear solution is formed. The solution is covered with aluminum foil. The Solvent is allowed to evaporate by piercing 5-6 fine holes in the foil. Entire process is carried out at room temperature with constant stirring. The product is dried at 60ºc for 5 minutes for the evaporation of solvent then the co-crystals are formed.

Co-crystals of Oxcarbazepine - Oxalic acid

Co-crystals of Oxcarbazepine - Tartaric acid



Co-crystals of Oxcarbazepine - Benzoic acid

Figure 2

Evaluation of Co-Crystals:

It includes the following tests

- Solubility
- Drug content
- *In-vitro* dissolution studies

Solubility studies:

The flask containing 10ml of HCL, Phosphate buffer (different pH) and distilledwater and dissolve the Co-crystal in excess quantity in it. The samples were placed ina magnetic stirrer at 37ºC for 1hr. The solution was analyzed by the UV-visible spectrophotometer.

Drug content:

Dissolved accurately weighed quantity of Co-crystals equivalent to 10mg in 10ml of methanol solvent. Further, 1ml of solution was taken and diluted suitably. The solution was then filtered through Whatman filter paper. The determination ofOxcarbazepine drug content was carried at 256 nm by UV-visible spectrophotometer. The % drug content was to be calculated

Drug content (%) = actual amount/ theoretical amount×100

Invitro dissolution studies of Co-Crystals:

In- vitro dissolution test was carried out by using USP type 2 apparatus 900ml of pH 6.8phosphate buffer is used as dissolution media and the paddle was rotated at 75rpm at temperature 37±0.5ºc. Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analyzed spectrophotometrically at lambda max of the drug.

***In-vitro* dissolution parameters of Co-Crystals:**

Table 3:

Medium	pH 6.8 phosphate buffer
Temperature	37±0.5ºC
Apparatus	USP type 2 (paddle)
RPM	75 RPM
Time interval	0,10,20,30,40,50,60 min

Method of Preparation of Extended-Release Tablets:

Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests.

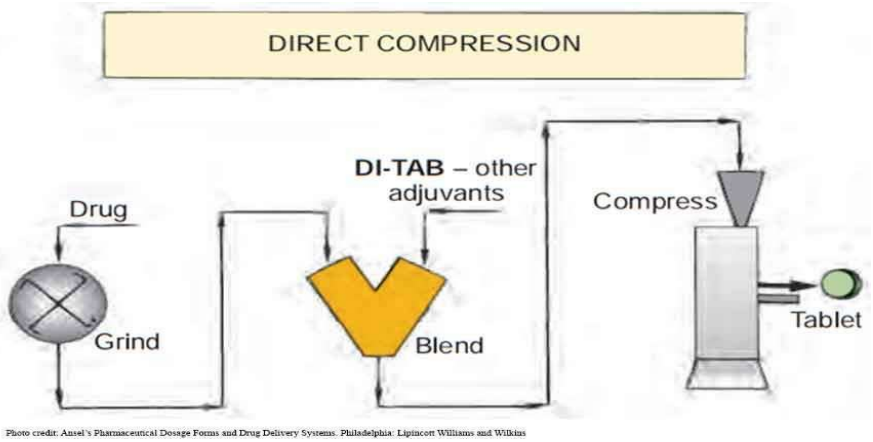


Figure 3: Method of Preparation of Extended-Release Tablets

FORMULATION DEVELOPMENT OF EXTENDED-RELEASE TABLETS:

Table 4: Formulation of Extended-release tablets:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Oxcarbazepine cocrystals	322.54	322.54	322.54	322.54	322.54	322.54	322.54	322.54	322.54
Chitosan	26	39	52	-	-	-	-	-	-
HPMC K10M	-	-	-	26	39	52	-	-	-
Carbopol 940	-	-	-	-	-	-	26	39	52
Microcrystallinecellulose	91.46	78.46	65.46	91.46	78.46	65.46	91.46	78.46	65.46
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	450	450	450	450	450	450	450	450	450

RESULTS AND DISCUSSION:

API Characterization: Organoleptic properties of Oxcarbazepine were carried out and the results were given in the **Table 5**.

Table 5: Organoleptic Properties of Oxcarbazepine

Parameter	Inference
Colour	White to faintly orange
Nature	Crystalline solid
Odour	Odourless
Taste	Tasteless
Melting point	215°c

Solubility:

The solubility studies of Oxcarbazepine pure drug were carried out in various solvents and the results were given.

Table 6: Solubility of Oxcarbazepine

Media	Solubility (mg/ml)
Distilled water	0.4388±0.03
Methanol	0.9762±0.25
0.1N HCL	0.3790±0.18
pH 6.8 phosphate buffer	0.810±0.31
pH 7.4 phosphate buffer	0.522±0.06

Analytical Method:

Construction of Standard Calibration Curve of Oxcarbazepine Pure drug:

The analytical method which was carried out using UV-Visible spectrophotometer, the maximum absorbance (λ max) of Oxcarbazepine in pH 6.8 phosphate buffer was found to be 256nm. Standard calibration curve was plotted.

Standard calibration curve of Oxcarbazepine in pH 6.8 phosphate buffer:

Table 7: Standard calibration curve

S.no	Concentration (µg/ml)	Absorbance (nm)
1.	2	0.217 ± 0.004
2.	4	0.313 ± 0.007
3.	6	0.592 ± 0.003
4.	8	0.801 ± 0.001
5.	10	0.942 ± 0.003

Note: All values were expressed as mean ± SD, n=3, SD=standard deviation

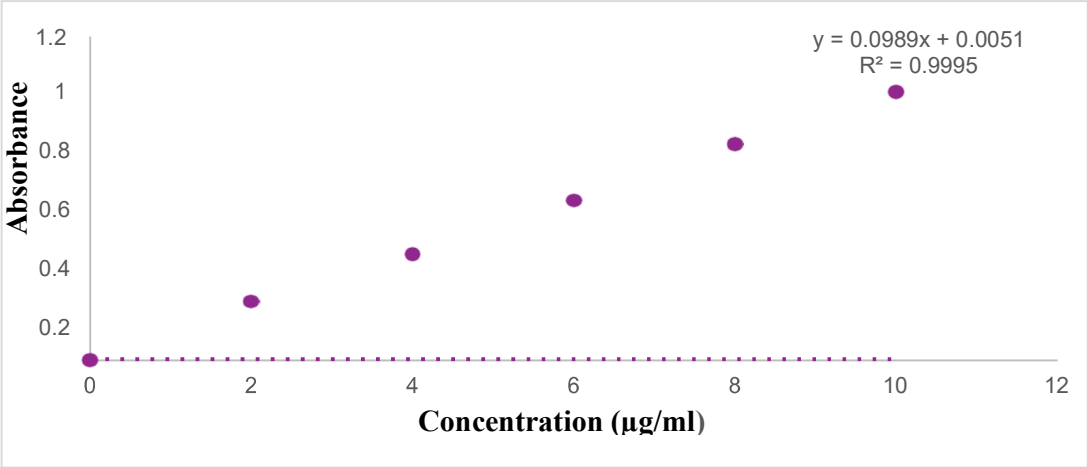


Figure 4: Standard calibration curve of Oxcarbazepine in pH 6.8 phosphate buffer

In-vitro dissolution studies of Oxcarbazepine Co-crystals

Table 8: In-vitro dissolution studies of Oxcarbazepine Co-crystals

S. No.	Time (min)	Percentage drug release					
		F1	F2	F3	F4	F5	F6
1.	10	21.39±0.33	26.35±0.27	14.22±0.19	15.10±0.73	30.31±0.10	25.99±0.08
2.	20	35.39±0.57	36.402±0.43	25.56±0.75	24.49±0.65	39.66±0.24	42.63±0.19
3.	30	44.04±0.48	47.672±0.38	36.24±0.32	38.41±0.29	54.18±0.56	52.97±0.78
4.	40	60.55±0.81	56.286±0.18	43.24±0.49	53.27±0.07	66.42±0.35	59.89±0.57
5.	50	72.3±0.32	74.1±0.05	57.33±0.26	63.42±0.21	79.56±0.58	64.88±0.07
6.	60	81.84±0.49	86.53±0.93	63.96±0.09	72.84±0.15	94.92±0.62	84.38±0.01

Note: All values were expressed as mean ± SD, n=3, SD=standard deviation

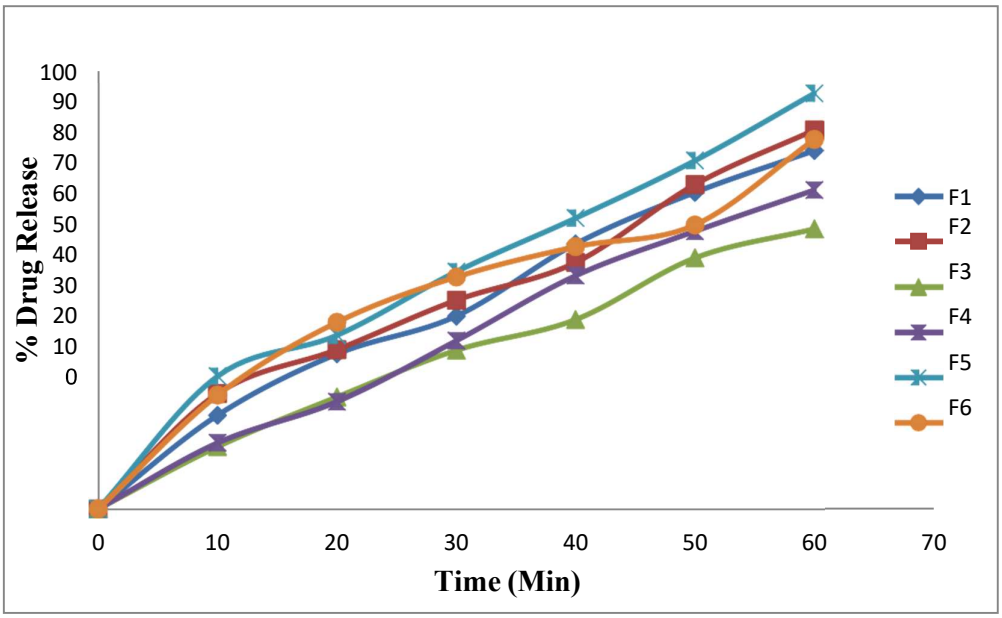


Figure 5: In-Vitro dissolution studies of Oxcarbazepine Co-crystals

In-vitro drug release studies details:

Table 9: *In-vitro* dissolution parameters of E.R Tablet

Apparatus used	USP XXIII dissolution Test apparatus
Dissolution medium	pH 6.8 phosphate buffer
Dissolution medium volume	900 ml
Temperature	37±5°C
Speed of basket paddle	75 rpm
Sampling intervals	30 min, 1hr, 1.5hrs, 2hrs, 2.5hrs, 3hrs, 4hrs, 5hrs, 6hrs, 7hrs, 8hrs
Sample withdraw	5 ml
Absorbance measured	256 nm

Evaluation tests of Oxcarbazepine Extended-release tablets:

Table 10: Pre compression Parameters of extended-Release Tablets

S.no	Formulation code	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
1.	F1	0.48±0.026	0.78±0.016	29.92±0.032	14.20±0.068	1.29±0.058
2.	F2	0.54±0.014	0.70±0.069	26.96±0.065	15.89±0.098	1.45±0.065
3.	F3	0.52±0.012	0.76±0.095	29.54±0.021	15.07±0.065	1.26±0.085
4.	F4	0.50±0.015	0.77±0.065	30.92±0.064	14.49±0.073	1.39±0.098
5.	F5	0.54±0.095	0.72±0.068	30.96±0.015	16.32±0.034	1.14±0.069
6.	F6	0.58±0.065	0.75±0.098	31.31±0.024	14.37±0.016	1.20±0.095
7.	F7	0.53±0.036	0.73±0.079	28.25±0.054	16.78±0.064	1.40±0.061
8.	F8	0.55±0.039	0.77±0.034	29.51±0.079	14.26±0.043	1.30±0.013
9.	F9	0.58±0.065	0.79±0.073	31.27±0.064	15.73±0.065	1.17±0.091

Note: All values were expressed as mean ± SD, n=3, SD = standard deviation

Table 11: Post compression Parameters of Extended-Release Tablets

S.no	Formulationcode	Hardness	Thickness	Friability	Weight variation	Drug content
1.	F1	4.0±0.11	3.13±0.02	0.36±0.04	447±1.8	93.13±0.88
2.	F2	4.3±0.63	3.21±0.07	0.44±0.06	449±0.3	97.76±0.83
3.	F3	4.5±0.16	2.98±0.24	0.53±0.03	450±1.9	94.77±0.87
4.	F4	4.0±0.19	3.01±0.05	0.69±0.35	449±1.2	96.20±0.64
5.	F5	3.9±0.21	3.08±0.03	0.33±0.09	448±0.9	92.89±0.58
6.	F6	4.2±0.30	2.96±0.02	0.63±0.06	450±1.5	95.12±0.42
7.	F7	4.6±0.26	3.11±0.05	0.51±0.10	447±1.1	94.30±0.5
8.	F8	4.2±0.18	3.15±0.14	0.62±0.13	449±0.6	93.20±0.8
9.	F9	4.5±0.16	3.21±0.07	0.63±0.05	448±0.3	95.89±0.69

Note: All values were expressed as mean ± SD, n=3, SD=standard deviation

Table 12: Invitro dissolution studies of Oxcarbazepine Extended-release Tablets

Time (hrs)	% Drug release of Oxcarbazepine extended-release tablets									
	RLD	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	9.99±0.31	8.66±0.48	11.40±0.17	8.04±0.34	4.46±0.12	4.15±0.28	6.00±0.35	6.95±0.15	7.39±0.36	6.34±0.36
1	16.49±0.22	11.60±0.32	20.07±0.23	9.62±0.43	8.15±0.35	6.04±0.43	10.04±0.55	11.36±0.31	8.66±0.25	11.62±0.26
1.5	23.11±0.13	21.04±0.25	25.08±0.19	14.10±0.37	11.93±0.24	10.48±0.31	10.30±0.30	15.48±0.47	15.28±0.45	15.99±0.25
2	33.03±0.25	26.27±0.29	38.18±0.37	21.46±0.21	16.13±0.32	13.15±0.36	17.73±0.26	23.53±0.27	24.08±0.41	20.79±0.47
2.5	34.59±0.31	33.58±0.17	47.82±0.45	25.63±0.25	18.49±0.29	17.45±0.16	22.07±0.41	26.46±0.25	28.04±0.36	25.96±0.27
3	46.93±0.25	37.24±0.46	53.01±0.41	35.70±0.16	24.12±0.32	22.71±0.34	26.93±0.40	32.30±0.41	32.67±0.55	35.71±0.48
4	54.82±0.43	42.39±0.26	58.82±0.25	48.13±0.43	26.86±0.41	27.49±0.28	32.38±0.26	36.73±0.26	37.97±0.15	41.33±0.45
5	61.78±0.14	44.75±0.29	66.52±0.29	53.11±0.35	35.85±0.35	37.23±0.55	36.55±0.37	43.55±0.45	46.36±0.26	43.37±0.51
6	69.62±0.26	52.98±0.52	72.72±0.46	62.33±0.37	38.99±0.36	46.36±0.15	44.25±0.48	48.42±0.51	50.92±0.32	50.57±0.55
7	76.37±0.39	58.63±0.14	80.20±0.24	62.50±0.26	44.50±0.29	51.20±0.47	51.02±0.57	54.30±0.32	65.25±0.38	56.00±0.35
8	80.51±0.16	69.50±0.42	82.45±0.13	74.36±0.34	48.31±0.34	56.20±0.25	63.97±0.48	56.31±0.26	75.77±0.25	69.44±0.32

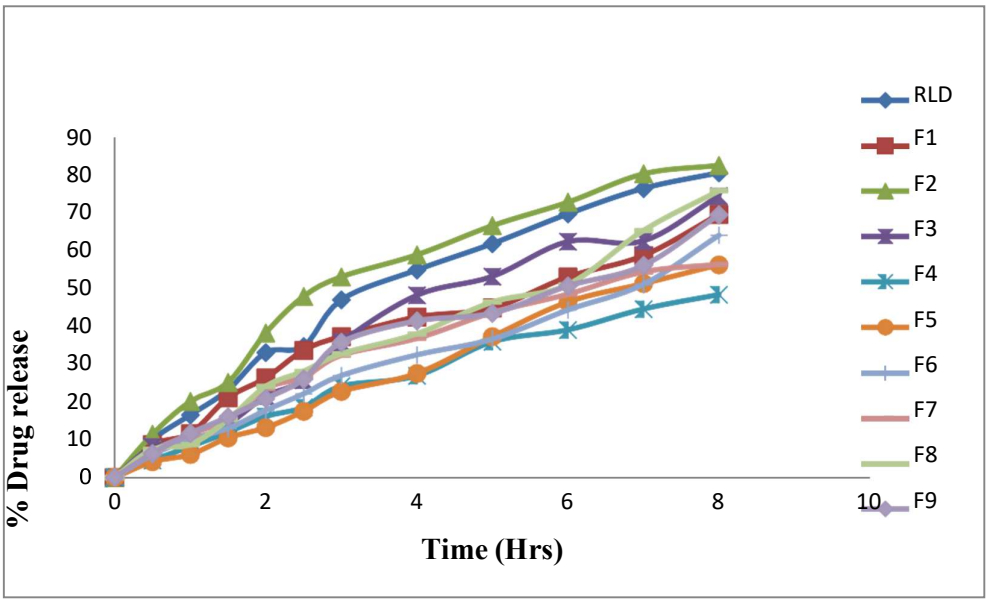


Figure 6: In-vitro dissolution studies of Oxcarbazepine Extended-release tablets

Stability studies of optimized formulation:

Table 13: Stability studies of optimized formulation

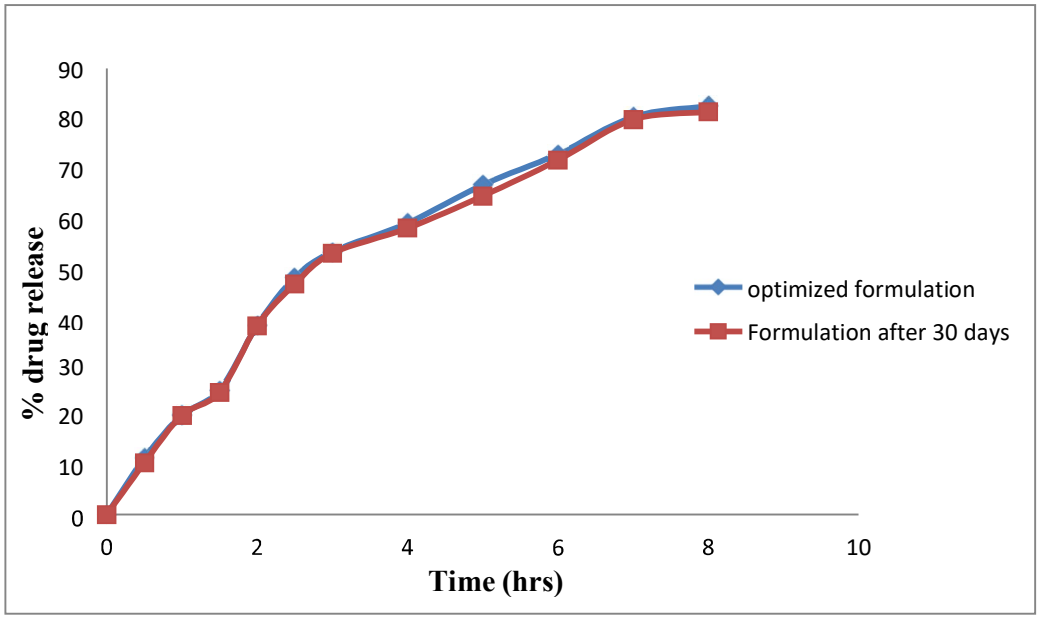
S.no	Parameters	Initial	After 1 month
1	Description	White to faintlyorange	White to faintlyorange
2	Weight	449.6	449.3
3	Hardness	4.3	4.0
4	Friability	0.44	0.40
5	Thickness	3.21	3.15
6	Dissolution	82.45	81.28

Stability Studies of Optimized formulation -Dissolution study:

Dissolution study of optimized formulation

Table 14: Dissolution study of optimized formulation

	Time (Hrs)	% Drug release of Oxcarbazepine Extended release tablet after storage	
		Initial	30^{th} day
1	0.5	11.40	10.46
2	1	20.07	20.04
3	1.5	25.08	24.66
4	2	38.18	38.12
5	2.5	47.82	46.53
6	3	53.01	52.74
7	4	58.82	57.80
8	5	66.52	64.29
9	6	72.72	71.54
10	7	80.20	79.65
11	8	82.45	81.28



CONCLUSION:

Co-crystals is one of the solubility enhancement techniques for the delivery of the poorly soluble drugs. Due to the low solubility of drug desired therapeutic action cannot be achieved. In order to enhance solubility co-crystal method is used to increase solubility. For the reduction of dosing frequency Oxcarbazepine was formulated as extended-release dosage form which controls the condition of epilepsy for a prolonged period of time. Oxcarbazepine co-crystals are prepared and which are further formulated into extended-release tablets. The Oxcarbazepine extended-release tablets were prepared by direct compression technique using different polymers like Chitosan, HPMCK10M, Carbopol 940 and the *In-vitro* drug release studies were carried out for 8 hrs. The formulation prepared by using 8% concentration of chitosan as rate retarding polymer which shows similarity to that of marketed product. Hence the further studies can be carried out for the estimation of the *In vitro –In vivo* correlation and the combination of the polymers to modulate the drug release rate for enhancing better patient compliance.

ACKNOWLEDGEMENT:

The authors would like to thank the school of pharmaceutical sciences & technologies, Institute of science and Technology, JNTUK for the facilities during doing this work.

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