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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF OXCARBAZEPINE USING DIFFERENT POLYMERS

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ABSTRACT

The aim of present investigation was to formulate and evaluate the sustained release tablets of Oxcarbazepine. These matrix tablets were prepared by direct compression method using natural polymers like Aloes Powder,Gum copal, Gum dammar. *In vitro* drug release studies were performed by USP dissolution apparatus type II using 0.1N HCL buffer and 6.8 Phosphate buffer for 12hrs. Among all the 12 formulations Formulation F9 showed maximum drug release 99.53% for 12hrs study. It was observed from the kinetic studies that all the formulation followed Peppas-Release kinetics.

KEYWORDS: Oxcarbazepine, Aloes Powder Gum copal, Gum dammar.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodymics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.[1,2]

Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.
- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.[3,4,5]

Recent trends in sustained drug delivery system
Sustained release dosage forms are categorized as

- Single unit dosage form.
- Multiple unit dosage form.
- Mucoadhesive system.

Single unit dosage form

These refer to diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film.

These systems can be classified as
Monolithic system

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is rate-limiting step.

These are categorized as
Hydrophobic/Swellable tablet

Tablet prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the

release time of the drug from device within the GI tract after oral administration.

Floating tablet or capsule
Designing of Floating tablet or capsule are called hydro-dynamically balanced drug delivery system is based on the principle that device with gravity lesser than that of the gastric juice of stomach and retain the drug in the proximal region of the GIT.

Semisolid matrix system
In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

Plan of Work
1. Literature Review
2. Selection of Drug and Excipients
3. construction of standard graph
4. pre formulation studies
5. preparation of powders
6. evaluation of powders
- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio
7. Compression of powders into tablets
8. Evaluation of tablets
- Thickness
- Hardness
- Friability
- Uniformity of weight
- Drug content
- In vitro dissolution
9. Drug and Excipient compatibility studies

Drug Profile
Drug: Oxcarbazepine
Drug category: Anti-epileptic Agent
Structure:

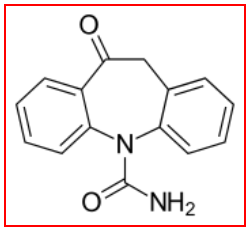

Fig: 1.

Chemical name/ Nomenclature / IUPAC Name: 5-oxo-6~{H}-benzo[b][1]benzazepine-11- Carboxamide.
Molecular Formula: $C_{15}H_{12}N_2O_2$
Molecular Weight: 252.273 g/mol
Official Pharmacopoeia: USP

Mechanism of action: The exact mechanism by which oxcarbazepine exerts its anticonvulsant effect is unknown. It is known that the pharmacological activity of oxcarbazepine occurs primarily through its 10-monohydroxy metabolite (MHD). In vitro studies indicate an MHD-induced blockade of voltage-sensitive sodium channels, resulting in stabilization of hyper excited neuronal membranes, inhibition of repetitive neuronal discharges, and diminution of propagation of synaptic impulses.

Analytical method development
a) Determination of absorption maxima
100mg of Oxcarbazepine pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve
100mg of Oxcarbazepine pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 10,20,30,40 and 50 µg/ml of Oxcarbazepine per ml of solution. The absorbance of the above dilutions was measured at 254 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

RESULTS AND DISCUSSION

Standard Calibration curve of Oxcarbazepine
Table 1: Concentration and absorbance obtained for calibration curve of Oxcarbazepine in 0.1 N hydrochloric acid buffer (pH 1.2).

Copncentration (µg/ml)	Absorbance(Au)
0	0
10	0.136
20	0.312
30	0.467
40	0.639
50	0.823

It was found that the estimation of Oxcarbazepineby UV spectrophotometric method at λ_{max}254 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study.

The correlation coefficient for the standard curve was found to be closer to 1, concentration range,10-50µg/ml.

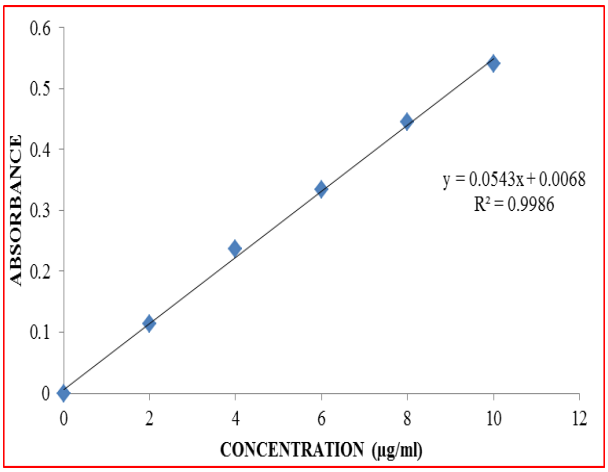

Fig. 2: Standard graph of Oxcarbazepine in 0.1 N HCl.

Table 2: Concentration and absorbance obtained for calibration curve of Oxcarbazepine in pH 6.8 Phosphate buffer.

Copncentration (µg/ml)	Absorbance(Au)
0	0
10	0.129
20	0.295
30	0.457
40	0.632
50	0.799

It was found that the estimation of Oxcarbazepine by UV spectrophotometric method at λ_{max}256 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 10-50µg/ml.

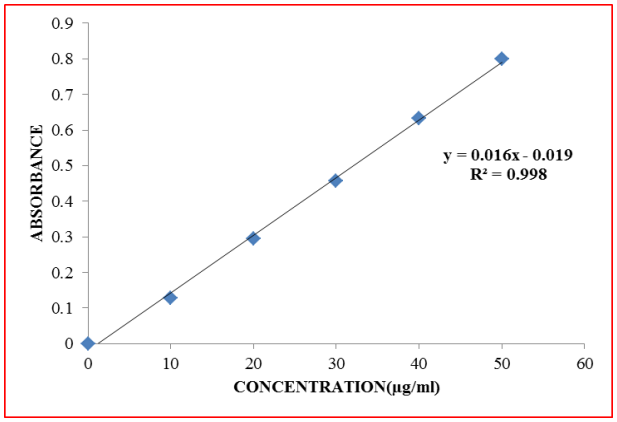

Fig. 3: Standard curve of Oxcarbazepine

Evaluation

Characterization of pre-compression blend

The pre-compression blend of oxcarbazepine were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 39.23˚, Carr's index values were less than 16.53 for the pre-compression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.195 for all batches indicating good flow properties.

Table 3: Physical properties of pre compression blend.

Batch No	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F1	0.525±0.11	0.619±0.02	15.32±0.09	1.197±0.07	35.24±0.07
F2	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06	36.27±0.06
F3	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13	34.65±0.08
F4	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02	33.54±0.04
F5	0.516±0.24	0.622±0.05	14.96±0.15	1.186±0.03	32.21±0.01
F6	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21	39.23±0.01
F7	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01	31.10±0.02
F8	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03	32.19±0.02
F9	0.517±1.05	0.617±0.03	15.66±0.10	1.185±0.15	33.28±0.01
F10	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01	30.86±0.03
F11	0.523±0.45	0.612±0.01	14.95±0.66	1.17±0.02	31.24±0.04
F12	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01	30.48±0.02

All the values represent n=3.

Evaluation of tablets

Physical evaluation of oxcarbazepine immediate release tablets: The results of the weight variation, hardness, thickness, friability, and drug content of tablets are given in table .All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit .The hardness of the tablets ranged from 4.41 -4.65 kg/cm^2 and the friability values were < than 0.51 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.21-2.46cm .All the formulations satisfied the content of the drug as they contained 98-100% of Oxcarbazepine and good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 4: Physical evaluation of Oxcarbazepine.

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	295.5	2.25	4.65	0.42	98.8
F2	296.2	2.39	4.55	0.38	99.4
F3	298.7	2.46	4.59	0.46	97.6
F4	300.2	2.35	4.48	0.42	98.2
F5	299.9	2.41	4.45	0.51	99.7
F6	301.1	2.44	4.56	0.43	98.3
F7	297.4	2.52	4.49	0.49	97.2
F8	299.8	2.29	4.52	0.44	99.5
F9	300.3	2.21	4.41	0.36	100.1
F10	298.7	2.42	4.49	0.39	97.7
F11	301.4	2.38	4.61	0.42	99.3
F12	299.0	2.24	4.56	0.45	98.6

***In-vitro* release studies**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 256nm.

Table 5: *In-vitro* data for formulation F1-F4.

TIME (HRS)	% DRUG RELEASE			
	F1	F2	F3	F4
Time	0	0	0	0
0.5	2.91	4.12	6.34	8.49
1	5.12	6.65	11.12	14.69
2	8.86	10.16	13.61	25.51
3	11.27	12.71	17.39	36.24
4	19.64	21.47	33.91	47.89
5	34.82	38.48	45.28	59.91
6	42.21	46.91	51.01	66.84
7	52.37	58.91	75.62	71.36
8	68.61	71.01	79.21	74.77
9	71.74	78.47	89.99	81.59
10	82.81	87.89	97.14	88.26
11	87.22	91.46		91.73
12	92.31	97.29		96.08

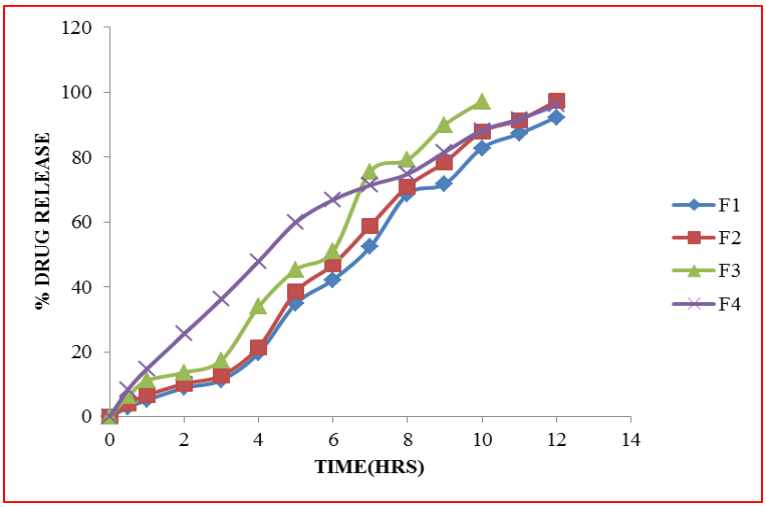

Fig. 4: *In vitro* dissolution data for formulation F1-F4.

Table 6: *In vitro* dissolution data for formulations F5-F8.

TIME (HRS)	% DRUG RELEASE			
	F5	F6	F7	F8
0	0	0	0	0
0.5	9.11	10.39	12.29	13.26
1	15.86	17.31	19.93	25.33
2	28.14	23.33	29.86	29.63
3	39.19	31.25	37.79	33.34
4	45.68	36.62	43.03	36.35
5	58.73	42.17	46.11	43.85
6	62.44	48.31	56.99	53.48
7	72.12	52.78	59.74	58.96
8	87.47	65.88	67.52	63.78
9	94.63	73.48	76.34	69.01
10		88.36	82.1	77.98
11		96.26	89.22	89.39
12			94.07	90.71

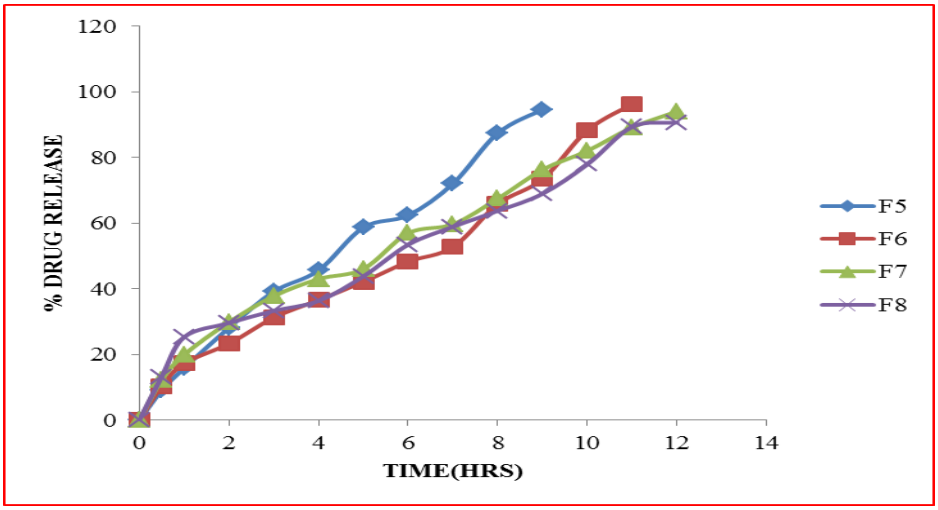

Fig. 5: *In vitro* dissolution data for formulations F5-F9.

Table 7: *In vitro* dissolution data for formulations F9-F12.

TIME(MIN)	% DRUG RELEASE			
	F9	F10	F11	F12
0	0	0	0	0
0.5	11.34	14.73	15.78	11.24
1	22.44	17.18	23.41	18.34
2	34.97	23.94	31.47	23.19
3	39.47	31.79	35.56	31.37
4	42.58	39.11	43.62	44.28
5	48.34	45.66	52.95	49.77
6	57.61	53.86	61.82	58.15
7	63.41	64.33	73.28	63.97
8	69.09	76.24	78.98	69.24
9	77.95	85.19	83.45	75.33
10	87.29	97.39	88.86	83.14
11	94.48		91.55	88.32
12	99.53		95.29	91.13

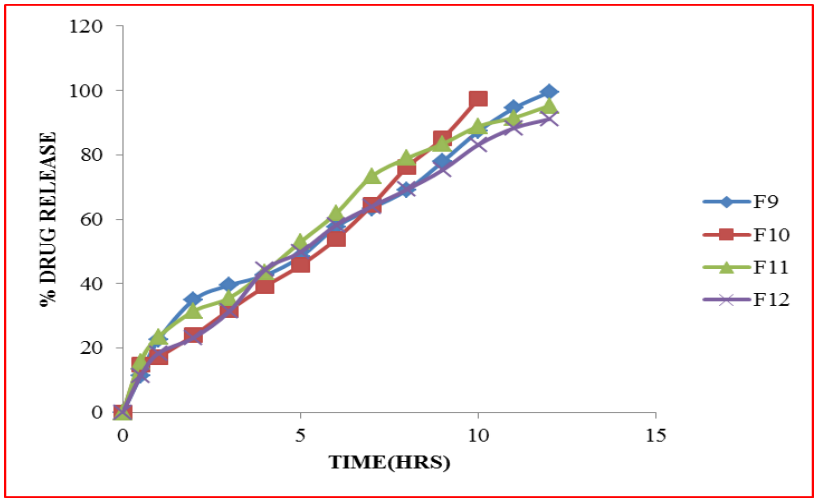

Fig. 6: *In vitro* dissolution data for formulations F9-F12.

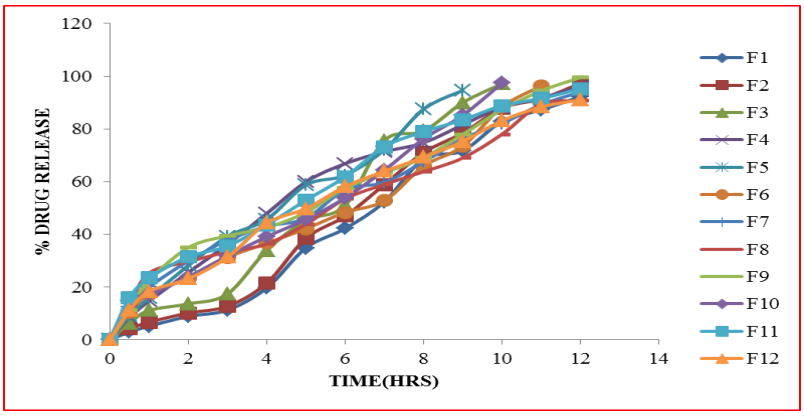

Fig. 7: *In vitro* dissolution data for formulations F1-F12.

Good result that is 99.53% in 12 Hours, at the concentration of 25 mg. Hence from all the formulations it is evident thatF9 formulation is the better formulation. The formulation is following zero order release kinetics.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Etodolac release. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyerpeppas mechanisms and the results were shown in below table**.**

Table 8: Release kinetics data for optimized formulation.

Cumulative (%) Release Q	Time (T)	Root (T)	Log (%) Release	LOG (T)	LOG (%) Remain	Releaserate (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
11.34	0.5	0.707	1.055	-0.301	1.948	22.680	0.0882	-0.945	88.66	4.642	4.459	0.183
22.44	1	1.000	1.351	0.000	1.890	22.440	0.0446	-0.649	77.56	4.642	4.265	0.377
34.97	2	1.414	1.544	0.301	1.813	17.485	0.0286	-0.456	65.03	4.642	4.021	0.620
39.47	3	1.732	1.596	0.477	1.782	13.157	0.0253	-0.404	60.53	4.642	3.926	0.715
42.58	4	2.000	1.629	0.602	1.759	10.645	0.0235	-0.371	57.42	4.642	3.858	0.784
48.34	5	2.236	1.684	0.699	1.713	9.668	0.0207	-0.316	51.66	4.642	3.724	0.917
57.61	6	2.449	1.760	0.778	1.627	9.602	0.0174	-0.240	42.39	4.642	3.487	1.155
63.41	7	2.646	1.802	0.845	1.563	9.059	0.0158	-0.198	36.59	4.642	3.320	1.322
69.09	8	2.828	1.839	0.903	1.490	8.636	0.0145	-0.161	30.91	4.642	3.138	1.503
77.95	9	3.000	1.892	0.954	1.343	8.661	0.0128	-0.108	22.05	4.642	2.804	1.837
87.29	10	3.162	1.941	1.000	1.104	8.729	0.0115	-0.059	12.71	4.642	2.334	2.308
94.48	11	3.317	1.975	1.041	0.742	8.589	0.0106	-0.025	5.52	4.642	1.767	2.874
99.53	12	3.464	1.998	1.079	-0.328	8.294	0.0100	-0.002	0.47	4.642	0.777	3.864

Table No.9: Formulation composition for tablets.

Ingrediants	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Oxcarbazepine	150	150	150	150	150	150	150	150	150	150	150	150
Aloes Powder	25	50	75	100	-	-	-	-	-	-	-	-
Gum copal	-	-	-	-	25	50	75	100	-	-	-	-
Gum dammar	-	-	-	-	-	-	-	-	25	50	75	100
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Lactose	119	94	69	44	119	94	69	44	119	94	69	44
Total weight	300	300	300	300	300	300	300	300	300	300	300	300

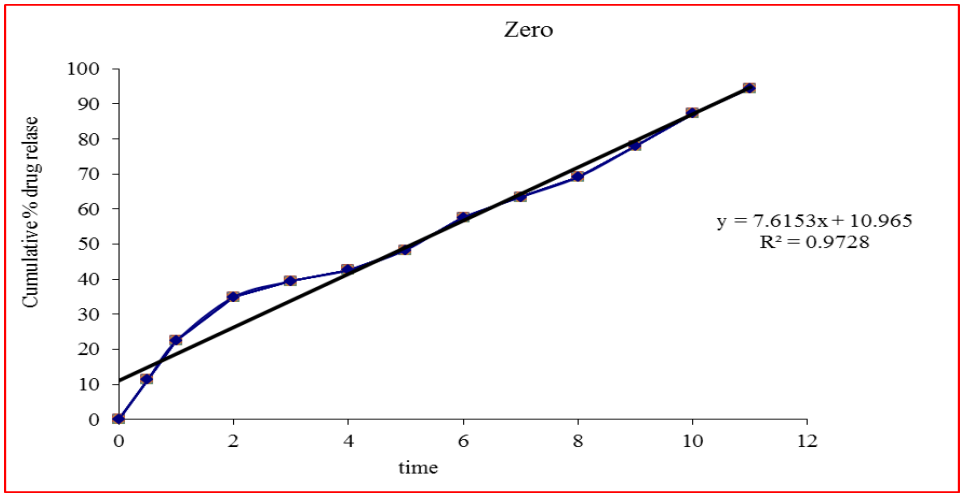

Figure 8: Graph of Zero Order kinetics.

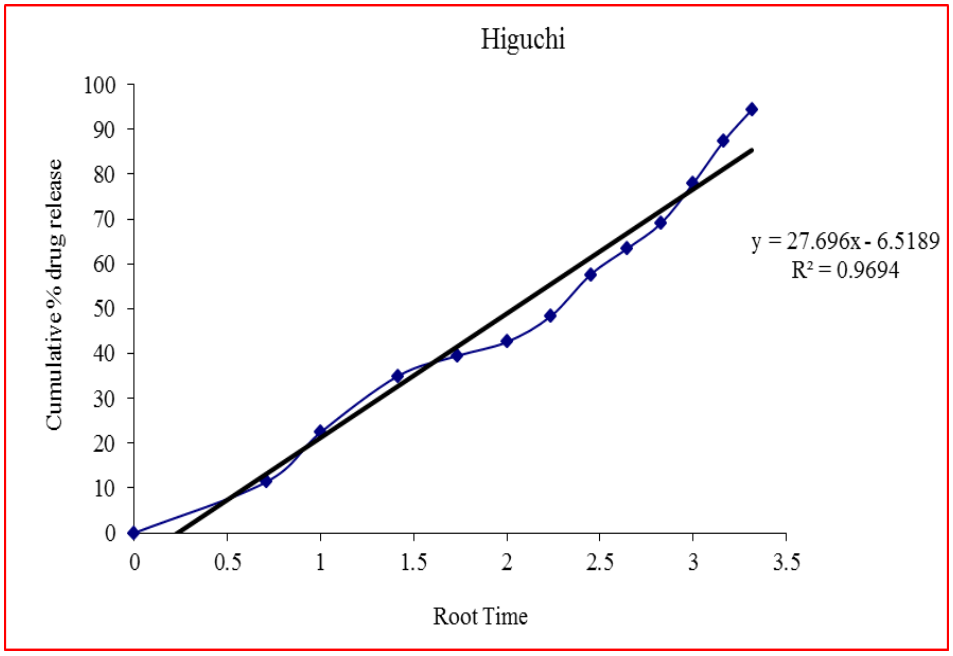

Figure 9: Graph of Higuchi Release kinetics.

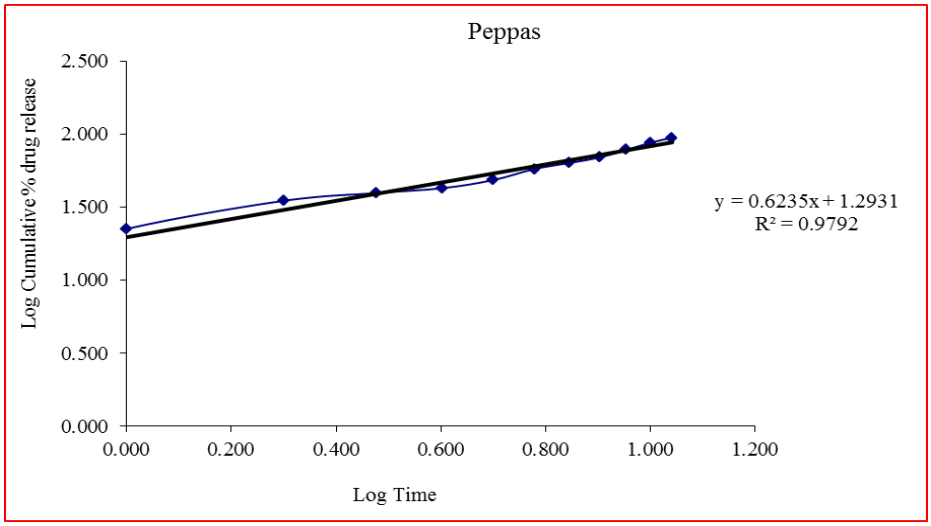

Figure 10: Graph of Peppas Release kinetics.

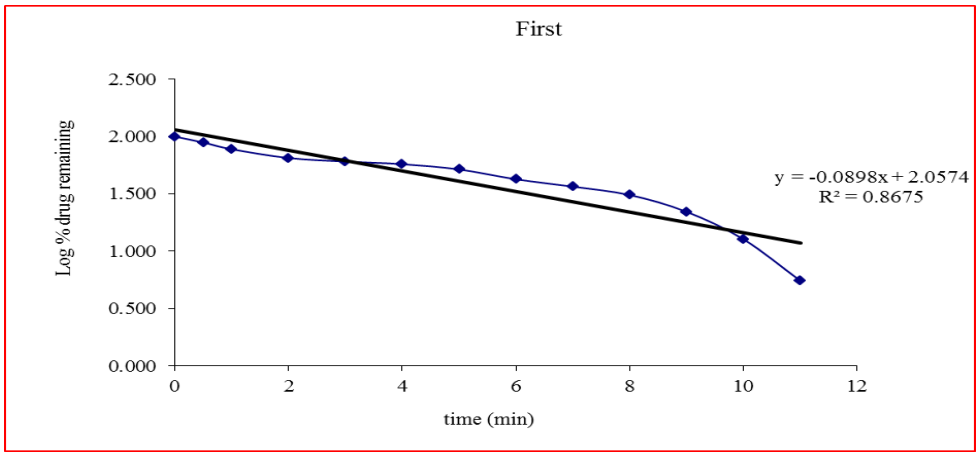

Figure 11: Graph of First Order Release Kinetics.

Based on the data above results the F9 optimized formulation followed Peppas Release kinetics.

Drug-Excipient compatibility studies by FTIR studies: Oxcarbazepinewas mixed with various proportions of excipients showed no color change at the end of two months, providing no drug –excipient interactions.

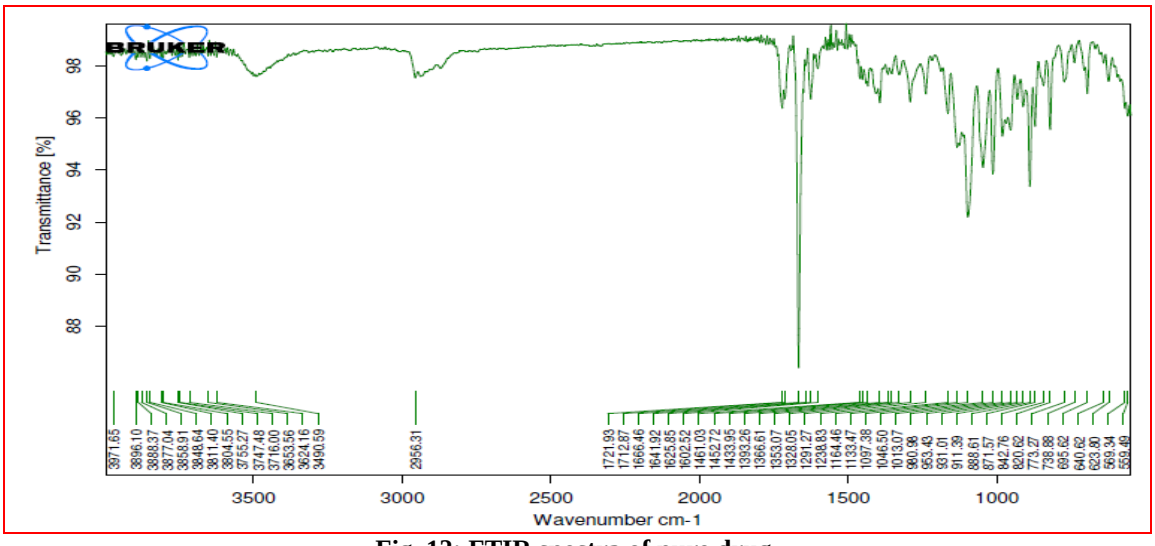

Fig. 12: FTIR spectra of pure drug.

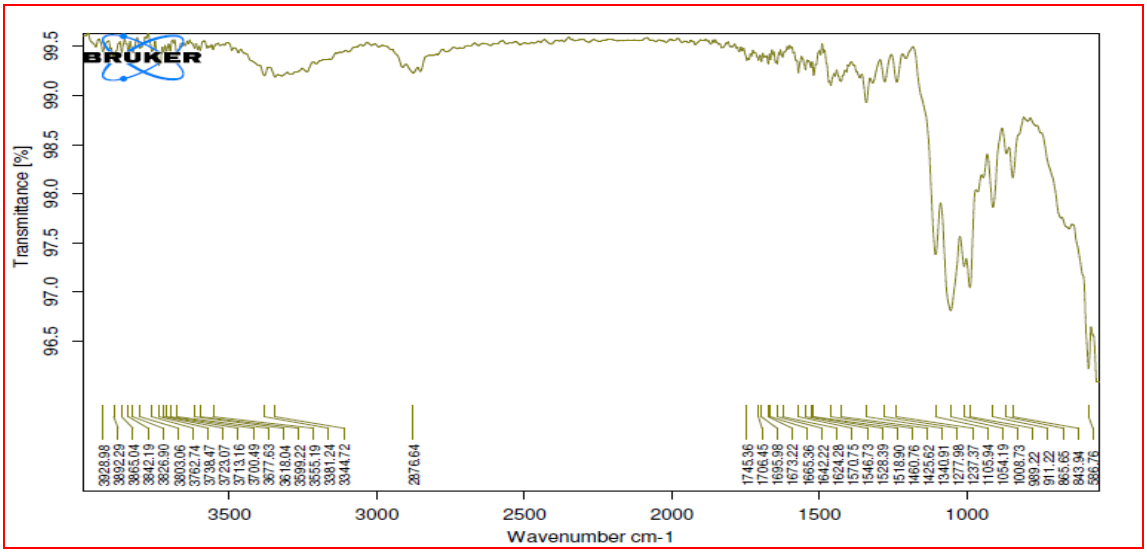

Fig. 13: FTIR spectra of optimized formulation.

CONCLUSION

In this study an effort was made to study SR Oxcarbazepine tablets which can provide sustained drug release for up to 12hrs. Oxcarbazepine SR tablets were formulated and evaluated. Oxcarbazepine SR tablets were prepared with different concentrations of Aloes Powder Gum copal, Gum dammar and were optimized by conducting various trials. Oxcarbazepine SR tablets with sustained drug release up to 12Hrs.

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