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DEVELOPMENT AND *IN VITRO* EVALUATION OF ONCE DAILY CARBAMAZEPINE MATRIX TABLET FROM HYDROPHILIC POLYMERS

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ABSTRACT: The purpose of study was to develop and characterize once daily extended release matrix tablets of Carbamazepine (CBZ), an antiepileptic drug. Tablets were prepared by wet granulation method. Methocel K15M CR and Methocel K100LV CR polymers were used as rate retarding agents in fourteen formulations. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, drug content etc. and showed satisfactory results. The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in vitro release studies. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications for tested parameters. The *in vitro* dissolution study was carried out for 24 hour in distilled water as the dissolution medium. The release mechanisms were explored and explained by Zero order, Higuchi, First order, Korsmeyer-Peppas and Hixson-Crowell equations. Primarily nine formulations were prepared by using three variable ratios of the two polymers, with 1% sodium lauryl sulphate. The optimized formulations F-5, F-6 and F-9 were further studied to know the effect of solubilizer on release by using various concentration of sodium lauryl sulphate and glyceryl mono stearate. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism followed anomalous type or non-Fickian transport and super case II transport. The release of drug was extended for 24 hour by polymer combinations which indicated the usefulness of the formulations for once daily dosage form. Besides, these studies explored both of the optimum concentration, effect of polymers and the use of sodium lauryl sulphate on CBZ release pattern from the tablet matrix for 24 hour period.

INTRODUCTION: CBZ is an antiepileptic drug and also used to treat trigeminal neuralgia. CBZ blocks sodium channel at therapeutic concentrations and inhibits high- frequency repetitive firing in neuron in culture. It also acts presynaptically to decrease synaptic transmission. These effects probably account for the anticonvulsant action of CBZ. The successful formulation to control drug for the required duration of time with optimum release mode depends on various factors, such as the physicochemical properties of the drug, the nature of drug-carrier matrix, the type of the dosage form and the route of administration [1]. To reduce the frequency of administration and to improve patient compliance, a once-daily extended-release formulation of CBZ is desirable [2-6].

For sustained release systems, the oral route of drug administration has, by far, received the most attention as it is natural, uncomplicated, convenient and safer route.[7] A number of methods and techniques have been used in the manufacturing of oral extended-release dosage forms. Probably the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix. The majority of oral drug delivery systems are matrix-based.

In such systems, the tablet is in the form of a compressed compact that contains an active ingredient, a lubricant, an excipient and a filler or binder. Erosion, diffusion and swelling of the matrix are the various methods through which the systems control drug delivery. The polymer properties invariably play an important role in the release pattern of the drug. If the polymer is predominantly hydrophilic, the swelling process chiefly controls the drug release. The swellable matrices are monolithic systems prepared by compressing a powdered mixture of a hydrophilic polymer and drug.

Matrix tablets composed of drug and release retarding material (e.g. polymer) offer the simplest approach in designing a sustained release system. Matrix tablets are prepared by either wet granulation or direct compression method. Currently available extended release matrix tablets are generally prepared by wet granulation method. CBZ extended release tablet matrix was prepared by wet granulation method using hydroxypropyl methylcellulose (HPMC). The polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of the polymers used [8].

There are number of techniques applied in the formulation and manufacturing of extended release dosage form. However, the matrix tablet by wet granulation has attracted much attention due to its technological simplicity in comparison with other controlled release systems. Wet granulation method has been applied for preparation of tablet matrix that high dose drugs that experience poor flow and/or poor compactibility can be granulated to obtain suitable flow and cohesion for compaction [9]. The release of drug from the tablet matrix depends on the nature of polymer.

Methocel K15M CR and Methocel K100LV CR, used in this study is hydrophilic polymer that become hydrated, swollen and facilitates to diffuse the drug. [10]

MATERIALS:

Drug: Carbamazepine (FIS, Italy);

Polymer: Methocel K15M CR, Methocel K100M LVCR (Colorcon, USA);

Other excipients: Sodium Lauryl Sulphate (SLS)(Weichers & Helm); Glyceryl monostearate (GMS) (Chemical Management Consortium(CMC); Germany); Colloidal Silicon Dioxide (Aerosil 200)(Degussa, Cobat, Germany.);Magnesium Stearate (Wilfrid Smith Ltd. UK.).

Solvents and reagents: Methanol (Merck, Germany); Methylene chloride (Merck, Germany); Distilled water.

METHODS:

Preparation of matrix tablets: Tablets were prepared by wet granulation technique. In formulation F-1 to F-9 (**Table 1**), active ingredient CBZ and release retardant Methocel K15M CR were blended together in a polybag for 10 minutes. Then, the blend was sieved through 0.425 mm mesh (SHIVA, India) and taken in a stainless still bowl. SLS was dissolved into 50 ml water. SLS solution was added with blend and mixed well to form granules. In the formulation F-10 to F-13 GMS was added with active ingredient and granules were prepared by same way.

Exception is the addition of purified water as granulating fluid instead of SLS solution. In the formulation F-14, active ingredient, release retardants Methocel K15M CR and GMS were blended together and form the granules by adding SLS solution. The granules were dried into a tray drier (Classic Scientific, India) at 60^{o}C. LOD of the granules were maintained within 0.80% to 1.20%. Finally the dried granules were sieved through 0.85 mm mesh then blended again with release retardant Methocel K100LVCR in a polybag for 5 minutes. The mix was blended (Laboratory designed small drum blender, China) finally with colloidal silicon dioxide (aerosol 200) and magnesium stearate (by passing through 0.425 mm mesh) for 1 minute and made into tablets by compression at a fixed compression force.

Tablets of 200 mg mass were compacted using a Clit Tablet Press (USA) with 8.9-mm flat circular punch and die sets. The compaction force was varied to obtain the desired hardness.

TABLE 1: PROPOSED FORMULATIONS OF CBZ MATRIX TABLETS

Formulation Code	CBZ	Methocel K15M CR	Methocel K100LV CR	SLS	GMS	Aerosil 200	Magnesium Stearate	Total Weight
F-1	200	44.12	44.12	2.94	--	1.47	1.47	294.12
F-2	200	41.10	26.40	2.74	--	1.37	1.37	273.98
F-3	200	38.46	12.82	2.56	--	1.28	1.28	256.4
F-4	200	27.40	41.10	2.74	--	1.37	1.37	273.98
F-5	200	25.64	25.64	2.56	--	1.28	1.28	256.4
F-6	200	24.10	12.05	2.41	--	1.21	1.21	240.98
F-7	200	28.82	38.46	2.56	--	1.28	1.28	256.4
F-8	200	12.05	24.10	2.41	--	1.21	1.21	240.98
F-9	200	11.36	11.36	2.27	--	1.14	1.14	227.27
F-10	200	25.64	25.64	--	2.56	1.28	1.28	256.4
F-11	200	24.10	12.05	--	2.41	1.21	1.21	240.98
F-12	200	11.36	11.36	--	2.27	1.14	1.14	227.27
F-13	200	25.64	25.64	1.28	1.28	1.28	1.28	256.4
F-14	200	25.32	25.32	--	--	1.27	1.27	253.18

Physical evaluation of Granules:

1. **Bulk density** [11]**:** LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by 40 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 50-ml measuring cylinder. After the initial volume was observed, the cylinder was placed into the tap density tester (Electrolab, India) and the machine was set to a fixed RPM. The reading of tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculated.

LBD = Weight of the powder / volume of the packing

TBD = Weight of the powder / Tapping volume of the packing

2. **Compressibility index** [12]**:** The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = {(TBD – LBD) X 100}/TBD

3. **Total porosity** [13]: Total porosity was determined by measuring the volume occupied by a selected weight of powder (V_{bulk}) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space (V)

Porosity (%) = $(V_{bulk} – V) / V_{bulk} \times 100$

4. **Angle of Repose** [14]: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Angle of Repose, $\vartheta = tan^{-1} h/r$

Where, h = Height of the powder cone, *r* = Radius of the powder cone.

5. **Moisture Content:** Amount of moisture present in the granules were determined by Karl Fischer titrator (Metrohm, Switzerland) according to the official method.

6. **Drug Content:** An accurately weighed amount of powdered CBZ (200 mg) was extracted with methanol and the solution was filtered through 0.45-µ membrane filter paper. The drug content was measured by HPLC with UV detector (SHIMADZU, Japan) at 230nm after suitable dilution with mobile phase (water: methanol: methylene chloride = 600:450:45) according to USP [15] (**Fig. 1, 2**).

Physical evaluation of Carbamazepine matrix tablet:

1. **Hardness and Friability:** For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (England) and the Roche friabilator (ERWEKA, Germany) respectively.

2. **Diameter and Thickness:** The diameter and thickness of the tablet was determined using digital vernier calipers (Neiko Tools, USA). Five tablets from each batch were used, and average values were calculated.

3. **Average weight and weight variation test:** To study average weight and weight variation, 20 tablets from each formulation were weighed using an analytical electronic balance (Sartorious, Germany) and the test were performed according to the official method.

4. **Drug content:** Ten tablets were weighed individually, and the drug was extracted with methanol. Drug content determined by the same way of granules.

5. **Dissolution studies:** The *in vitro* dissolution study was carried out using USP Type I dissolution apparatus (Electrolab, India). The study was carried out in 900 ml of distilled water. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37°C ± 0.5°C. Basket rotation was adjusted to 100 rpm. At definite intervals, 5 ml sample was withdrawn and analyzed spectrophotometricaly at 285 nm for the drug release by using UV-visible spectrophotometer (Shimadzu, UV-1601, Japan). At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.

6. **Kinetic treatment of dissolution data** [16-20]**:** In order to describe the kinetics of the release process of drug in the different formulations, zero-order ($Q_t = Q_0 + K_0t$), first- order ($\ln Q_t = \ln Q_0 + K_1t$), Higuchi ($Q_t = K_Ht^{1/2}$) and Korsmeyer- Peppas ($Qt/Q\infty = Kt^n$) and Hixson-Crowell models ($Q_0^{1/3} - Q_t^{1/3} = k_{HC} \times t$) were fitted to the dissolution data of optimized formulations using linear regression analysis. A value of n = 0.5 indicates case I (Fickian) diffusion or square root of time kinetics, 0.5<n<1 anomalous (non- Fickian) diffusion, n=1 Case –II transport and n>1 Super Case II transport.

RESULTS AND DISCUSSION: The results of angle of repose indicated good flow properties of the granules which was further supported by lower compressibility index values. The percentage porosity values of the granules indicated that the packing of the granules might range from close to loose packing and also further confirming that the particles were not of greatly different sizes. The drug content in a weighed amount of granules of all formulations indicated that the granules possessed satisfactory flow properties, compressibility and drug content [21].

The granules of different formulations were evaluated for angle of repose 23.75±0.01 to 32.01±0.040, generally values of angle of repose are rarely less than 20^o and values up to 40^o indicate reasonable flow properties. Loose bulk density 0.405±0.02 to 0.471± 0.04g/ml, tapped bulk density 0.468±0.03 to 0.570±0.06 g/ml. Compressibility index 10.66±0.04 to 19.47±0.015%,generally, compressibility index values upto 15% result in good to excellent flow properties, but readings above 25% indicates poor flowability. Moisture content 0.88 to 1.12%, total porosity 9.756± 0.04 to 19.44±0.03% and assay 98.10±0.02 to 101.4± 0.04% (**Table 2**). All the results were found within the limits.

The formulated matrix tablets met the pharmacopoeial requirement of uniformity of weight. All the tablets conformed to the requirement of drug content, as per USP. Hardness, % friability; diameter and thickness, tensile strength were well within acceptable limits (**Table 3**). All formulations showed less than 1% (w/w) friability that indicates the ability of tablets to withstand shocks which may be encountered during transport. The manufactured tablets showed low weight variations and a high degree of drug content uniformity was found among different batches of the tablets, and drug content was more than 98%.

TABLE 2: PROPERTIES OF GRANULES OF CBZ AND EXCIPIENTS

Formulation Code	Angle of Repose (°)	Loose Bulk Density (LBD) (g/mL)	Tapped Bulk Density (TBD) (g/mL)	Compressibilty Index (%)	Moisture content (%)	Drug content (%)	Total Porosity (%)
F-1	28.07±0.02	0.418±0.03	0.505±0.03	17.23±0.02	1.01	101.4±0.04	17.14±0.01
F-2	26.57±0.05	0.405±0.02	0.500±0.01	19.00±0.03	0.98	99.20±0.03	18.96±0.04
F-3	28.1±0.03	0.461±0.05	0.539±0.05	14.31±0.01	1.12	101.2±0.02	14.29±0.02
F-4	23.75 0.01	0.446±0.02	0.539±0.02	17.25±0.06	1.05	100.4±0.06	17.14±0.05
F-5	29.98±0.01	0.458±0.03	0.540± 0.01	15.03±0.04	1.01	99.60±0.05	15.15±0.06
F-6	25.17±0.03	0.459±0.011	0.570±0.06	19.47± 0.015	1.11	98.10±0.02	19.44± 0.03
F-7	27.07±0.02	0.471± 0.04	0.569± 0.04	17.22±0.06	1.07	99.50±0.04	17.24±0.03
F-8	26.32 0.06	0.450±0.03	0.548±0.05	17.88±0.05	1.09	100.6±0.01	17.86±0.05
F-9	28.01± 0.04	0.469±0.02	0.525±0.03	10.66± 0.04	1.06	100.1±0.03	10.71±0.06
F-10	32.01±0.04	0.409±0.03	0.478±0.02	14.44±0.011	0.96	99.23±0.05	12.50±0.01
F-11	30.96±0.06	0.405±0.02	0.468±0.03	13.46± 0.012	0.89	98.68±0.02	9.756± 0.04
F-12	29.73±0.02	0.449±0.02	0.518±0.04	13.32±0.03	1.03	99.26±0.02	13.33±0.04
F-13	31.05± 0.01	0.423±0.03	0.497± 0.03	14.89±0.01	1.12	99.68±0.04	11.11±0.01
F-14	28.92±0.05	0.416±0.02	0.493±0.01	15.62±0.02	0.88	100.2±0.01	15.38±0.03

TABLE 3: PROPERTIES OF CBZ MATRIX TABLETS

Formulation Code	Average Weight (mg)	Weight Variation (%)	Diameter (mm)	Thickness (mm)	Hardness (Newton)	Friability (%)	Assay (%)
F-1	294.4±0.02	2.25±0.03	8.9±0.01	4.40±0.03	150-180	0.23	99.45±0.02
F-2	274.5±0.04	2.10±0.02	8.9±0.03	4.20±0.04	150-180	0.45	98.65±0.06
F-3	256.6±0.06	2.30±0.06	8.9±0.04	4.00±0.05	120-150	0.31	98.07±0.02
F-4	274.2±0.03	2.75±0.02	8.9±0.04	4.20±0.03	130-160	0.36	99.15±0.03
F-5	256.6±0.05	1.20±0.04	8.9±0.02	4.00±0.01	150-180	0.31	98.03±0.02
F-6	240.7±0.01	1.50±0.03	8.9±0.01	3.70±0.03	110-125	0.27	101.6±0.04
F-7	255.7±0.03	1.30±0.1	8.9±0.05	4.00±0.03	120-150	0.29	98.26±0.02
F-8	241.6±0.02	2.20±0.01	8.9±0.02	3.70±0.01	110-135	0.39	98.60±0.03
F-9	226.7±0.06	2.25±0.05	8.9±0.03	3.60±0.04	100-120	0.36	99.26±0.06
F-10	256.8±0.02	2.20±0.06	8.9±0.06	4.00±0.02	100-135	0.41	98.07±0.05
F-11	241.2±0.06	2.75±0.01	8.9±0.05	3.70±0.02	130-150	0.45	99.67±0.03
F-12	227.3±0.01	1.25±0.06	8.9±0.01	3.60±0.06	120-140	0.29	98.99±0.02
F-13	256.7±0.05	1.50±0.03	8.9±0.03	4.00±0.02	120-140	0.27	100.1±0.01
F-14	253.4±0.02	1.30±0.02	8.9±0.02	3.90±0.06	100-125	0.25	99.13±0.04

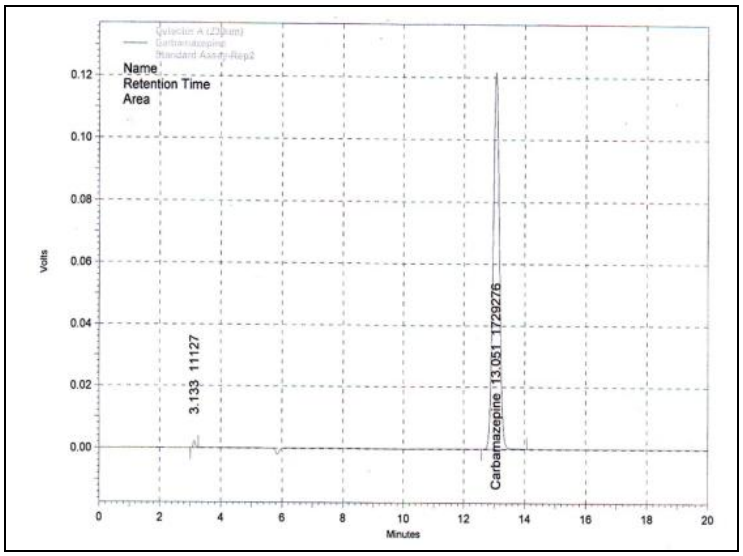

FIGURE 1: CHROMATOGRAM OF CBZ STANDARD SOLUTION

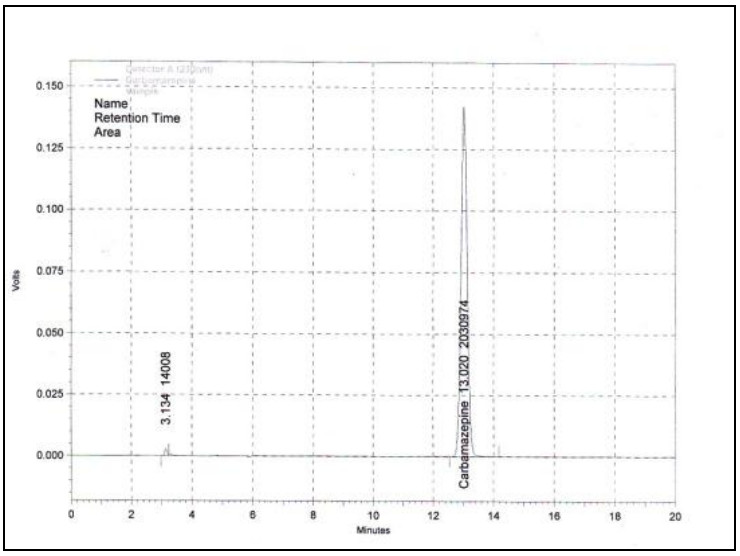

FIGURE 2: CHROMATOGRAM OF CBZ SAMPLE SOLUTION

TABLE: 4. RELEASE RATE CONSTANTS AND R^2 VALUES FOR DIFFERENT RELEASE KINETICS OF CBZMATRIX TABLETS

Formulation Code	Zero order		Higuchi		First order		Korsmeyer- Peppas		Hixson- Crowell	
	K_0	R^2	K_h	R^2	K_1	R^2	n	R^2	K_{HC}	R^2
F-1	2.39	0.834	12.89	0.915	0.015	0.892	1.343	0.913	-0.138	0.636
F-2	2.68	0.841	14.44	0.922	0.018	0.907	1.058	0.941	-0.136	0.624
F-3	3.59	0.839	19.55	0.949	0.036	0.929	0.712	0.969	-0.138	0.565
F-4	3.02	0.847	16.48	0.959	-0.024	0.955	0.740	0.958	-0.131	0.562
F-5	3.59	0.836	23.29	0.929	-0.069	0.981	1.069	0.932	-0.159	0.613
F-6	4.23	0.851	23.02	0.966	-0.100	0.956	0.902	0.943	-0.152	0.586
F-7	4.58	0.759	25.79	0.913	-0.089	0.975	0.950	0.903	-0.157	0.548
F-8	4.47	0.731	25.40	0.897	-0.088	0.975	0.899	0.901	-0.154	0.534
F-9	3.98	0.842	21.82	0.961	-0.056	0.997	0.844	0.937	-0.147	0.566
F-10	4.15	0.867	22.01	0.926	-0.050	0.978	1.955	0.942	-0.162	0.652
F-11	3.85	0.849	20.72	0.929	-0.039	0.961	1.165	0.927	-0.156	0.626
F-12	3.79	0.826	20.75	0.941	-0.041	0.956	0.959	0.925	-0.148	0.588
F-13	3.25	0.857	15.48	0.953	-0.027	0.964	0.957	0939	-0.141	0.597
F-14	2.96	0.918	15.48	0.953	-0.022	0.984	1.265	0.931	-0.146	0.665

In vitro dissolution studies indicated a steady state sustained release pattern throughout 24 hour of the study which was comparable to theoretical release profile. Drug release kinetics indicated that the drug release was best explained by Higuchi's equation and First order equation as these plots showed the highest linearity.

In the present study, nine formulations were formulated primarily by using three variable ratio of two polymers; Methocel K15M CRand Methocel K100 LV CR where all the formulation (F-1 to F-9) contained 1% sodium lauryl sulphate. Among these nine formulations only three formulations; F-5, F-6 and F-9 were met the official specification of release profile.

To determine the effect of solubilizer on the release of Carbamazepine matrix tablets, these three formulations were further studied by using equal percentage of glyceryl mono stearate another solubilizing agent instead of sodium lauryl sulphate .

From these three formulations, only formulation F-10 met the official specification of release profile however inferior than formulation F-5. Formulation F-13 contained equal amount of SLS and GMS did not follow the official specification of release profile. Formulation F-14 was free from solubilizer or surfactant did not follow the official specification of release profile also. (**Fig. 8**).

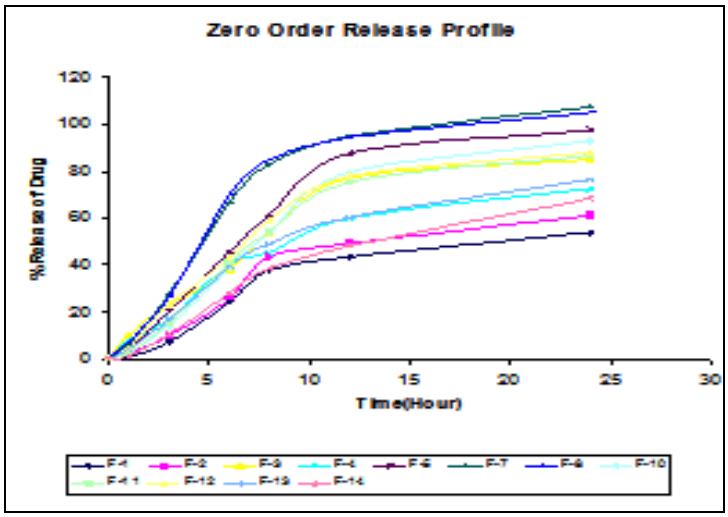

FIGURE 3: ZERO ORDER PLOT OF RELEASE KINETICS OF FOURTEEN FORMULATIONS (F-1 TO F-14) OF CBZ MATRIX TABLETS

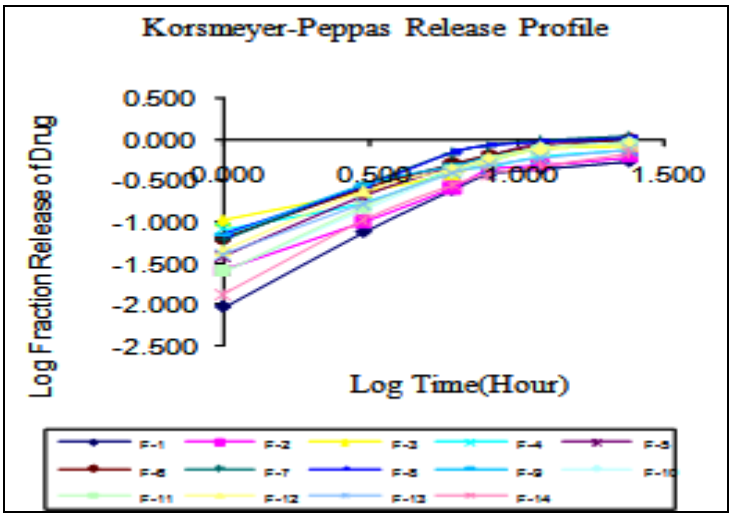

FIGURE: 6: KORSMEYER-PEPPAS PLOT OF RELEASE KINETICS OF FOURTEEN FORMULATIONS (F-1 TO F-14) OF CBZ MATRIX TABLETS

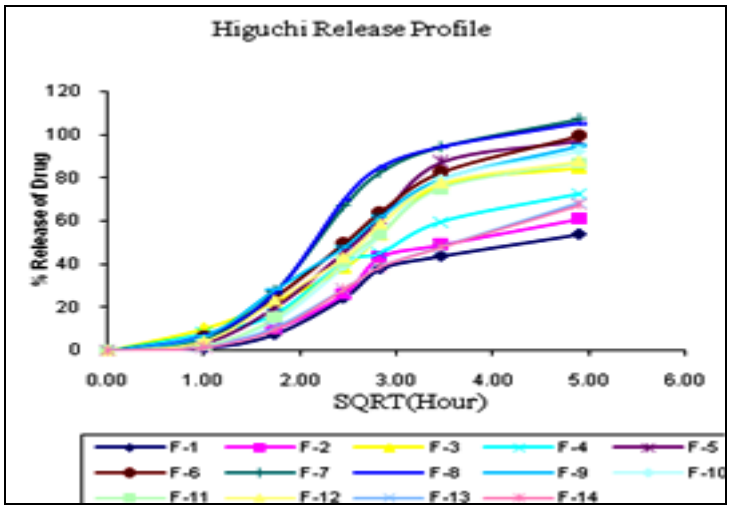

FIGURE 4: HIGUCHI PLOT OF RELEASE KINETICS OF FOURTEEN FORMULATIONS (F-1 TO F-14) OF CBZ MATRIX TABLETS

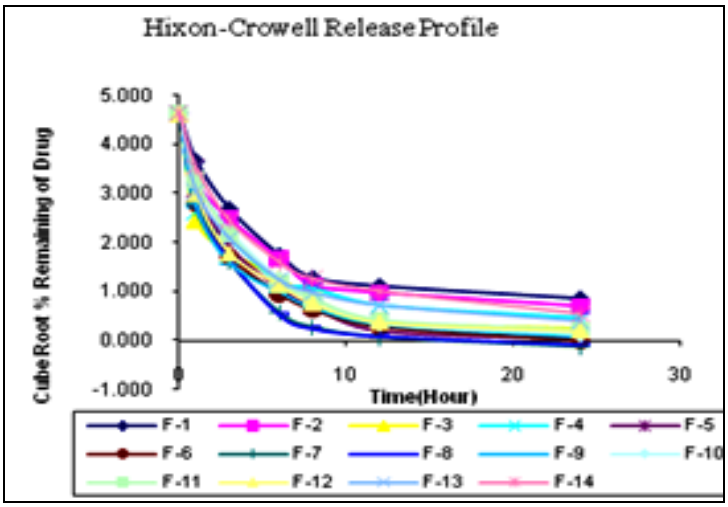

FIGURE 7: HIXSON-CROWELL PLOT OF RELEASE KINETICS OF FOURTEEN FORMULATIONS (F-1 TO F-14) OF CBZ MATRIX TABLETS

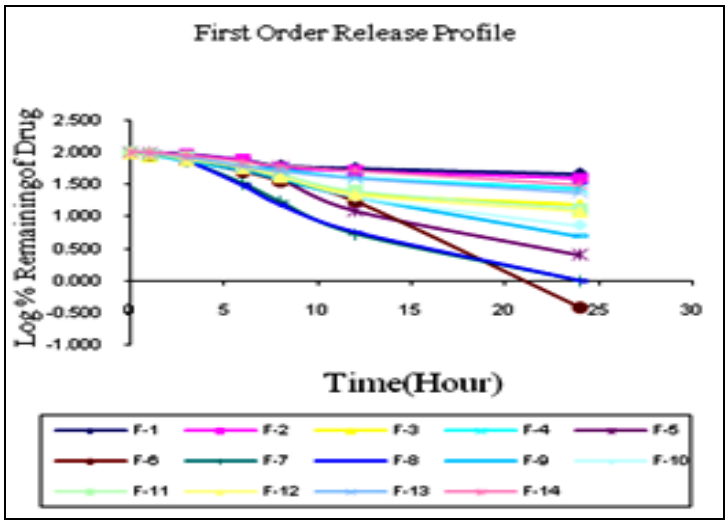

FIGURE 5: FIRST ORDER PLOT OF RELEASE KINETICS OF FOURTEEN FORMULATIONS (F-1 TO F-14) OF CBZ MATRIX TABLET

FIGURE 8: IMPACT OF SOLUBILIZER (SLS & GMS) ON THE RELEASE (F-5, F-10, F-13 AND F-14) OF CBZ MATRIX TABLETS

CONCLUSION: From these above discussion it was clear that the equal ratio of two polymers (10%: 10%) had good interaction with CBZ, that's why gave better release and sodium lauryl sulphate had better solubilizing property on Carbamazepine matrix tablet in compared to glyceryl mono stearate. Another finding was that blending of solubilizer (SLS and GMS) and without solubilizer or surfactant CBZ did not show desire or optimum release profile after 24 hour.

Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism followed anomalous type or non-Fickian transport and super case II transport which was dependent on the type and amount of polymer used. The drug release followed mainly super case II transport (n>0.85) (F-5, F-6, F-10), anomalous or non-Fickian transport (n>0.43 and n<0.85) in formulation F-9. The release of drug was extended for 24 hour by polymer combinations which indicated the usefulness of the formulations for once daily dosage forms. The optimized formulations may be used for the development of CBZ extended release tablet for commercial production in order to combat epilepsy and treatment of partial and tonic-clonic seizures.

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