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A STUDY ON FORMULATE AND EVALUATE OLMESARTAN MEDOXOMIL FLOATING CONTROLLED RELEASE TABLETS

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INTRODUCTION

Development of controlled release oral drug delivery system (CRDDS) by overcoming physiological adversities like short gastric residence timesand unpredictable gastric emptying times. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. controlledrelease gastro retentive dosage form (CRGRDFS or GRDDS).[4]

Controlled release Gastroretentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a prolonged period of time and thereby improved the bioavailability. GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.[5]

Need for controlled release Gastroretentive Drug Delivery Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as[6] –This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

FACTORS AFFECTING GASTRIC RETENTION

The gastric retention time (GRT) of dosage form is controlled by several factors, which affect their efficacy as a gastroretentive system.

- Density – GRT is a function of dosage form buoyancy that is dependent on the density.[12]
- Size – Dosage form units with a diameter of more than 9.5mm are reported to have an increased GRT.[13]
- Shape of dosage form – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.
- Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

METHODOLOGY

STANDARD GRAPH FOR OLMESARTAN MEDOXOMIL

The UV scanning of drug sample was carried out using a solution of drug dissolved in methanol solution at concentration of 100 µg/ ml. The λmax was observed at

255.6nm. The calibration curve of Olmesartan medoxomil was obtained by dissolving the drug in methanol solutions and absorbance was measured at 255.6nm in Methanol solution used as blank. Beer‟s law was obeyed the concentration range of 5-25 µg in methanol solution.

Method of preparation of 0.1N HCl
8.5 ml of Hydrochloric acid in 1000ml of water.

Preparation of Olmesartan medoxomil by Procedure of DirectCompression
Raw material → weighing → screening → Mixing → Compression.

MASTER FORMULATION
Table. 6: Master Formulation.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	40	40	40	40	40	40	40	40	40
HPMC K4M	20	30	40	-	-	-	-	-	-
HPMC K100	-	-	-	20	30	40	-	-	-
HPMC K15m	-	-	-	-	-	-	20	30	40
Mannitol	113	103	93	113	103	93	113	103	93
NaHCO3	15	15	15	15	15	15	15	15	15
MS	8	8	8	8	8	8	8	8	8
Talc	4	4	4	4	4	4	4	4	4
Total wt of Tablet	200	200	200	200	200	200	200	200	200

Ingredients	F10	F11	F12	F13	F14	F15
Drug	40	40	40	40	40	40
HPC	20	30	40	--	--	--
Carbopol	--	--	--	20	30	40
Mannitol	113	103	93	113	103	93
NaHCO3	15	15	15	15	15	15
MS	8	8	8	8	8	8
Talc	4	4	4	4	4	4
Total weight of tablet	200	200	200	200	200	200

FOURIER TRANSFORM INFRARED SPECTROSCOPY STUDIES
Principle
Electromagnetic radiation ranging between 500cm-1 and 4000cm-1 is passed through a sample and is absorbed by the bondes of themolecules in the sample causing them to stretch or bend. The wave length of the radiation absorbed is characteristic of the bond absorbing it.[16]

Table 10: FT IR absorption peaks.

Region	Wavelength(µm)	Wave number(cm-1)
Near IR	0.78-2.5	12500-4000
Mid IR	2.5-25.0	4000-400
Far IR	25-200	400-10

EQUIPMENT DETAILS
Manufacture: Shimadzu Software: IR affinity 1.
The mid IR region of analytical importance. FT IR spectroscopy is used to determine the functional groups in the drug molecule. We can elucidate the structure of drugs. Mainly it is used for structural elucidation. Based on the drug given in figure 21 and the optimized formulation given in figure 25, comparing the spectrum in both we conclude that the spectrums are correlated with each other.

Table 11: Fourier Transform Infrared Spectroscopy.

S.No	Peaks	Functional group
1	3668.62 & 3346.30	OH (Alcohol)
2	3051.96	Aromatic C-H Stretching
3	3015.42	Alkene C-H Stretching
4	2950.80 & 2893.72	Alkane C-H Stretching
5	1730.91 & 1709.46	Ketone
6	1621.74	NH (Amine)
7	1396.31, 1372.09, 1351.93 & 1325.98	C-O (Phenol)
8	1081.22, 1159.04, 1182.78	C-N Vibrations
9	600-900	C-H Bending (Aromatic)

Procedure

In the present study, potassium bromide pellet method was employed. The sample are thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc using dies. The disc was placed in the spectrophotometer and the spectrum was recorded.

Determination of floating parameter Buoyancy Studies

The time required for the tablet to rise to the surface and float was determined as Floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the Total floating time.

The in vitro floating behavior of the tablets was studied by placing them in 900 ml of plastic containers filled with 500 ml of 0.1 N HCl (pH 1.2, 37.5oC). The floating lag times and floating durations of thetablets were determined by visual observation.

Fig. 2: Floating tablet in 0.1N Hcl showing floating lag time.

Fig. 3: Floating tablet in 0.1N Hcl showing Total floating time.

KINETIC STUDIES

A. Zero Order Release Equation The equation for zero order release isQt = Q0 + K0 t

Where

Q0 = initial amount of drug

Qt = cumulative amount of drug release at time "t"K0 = zero order release constantt = time in hours.

It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.

- A graph is plotted between the time taken on x-axis and the cumulative percentage of drug release on y- axis and it gives a straight line.

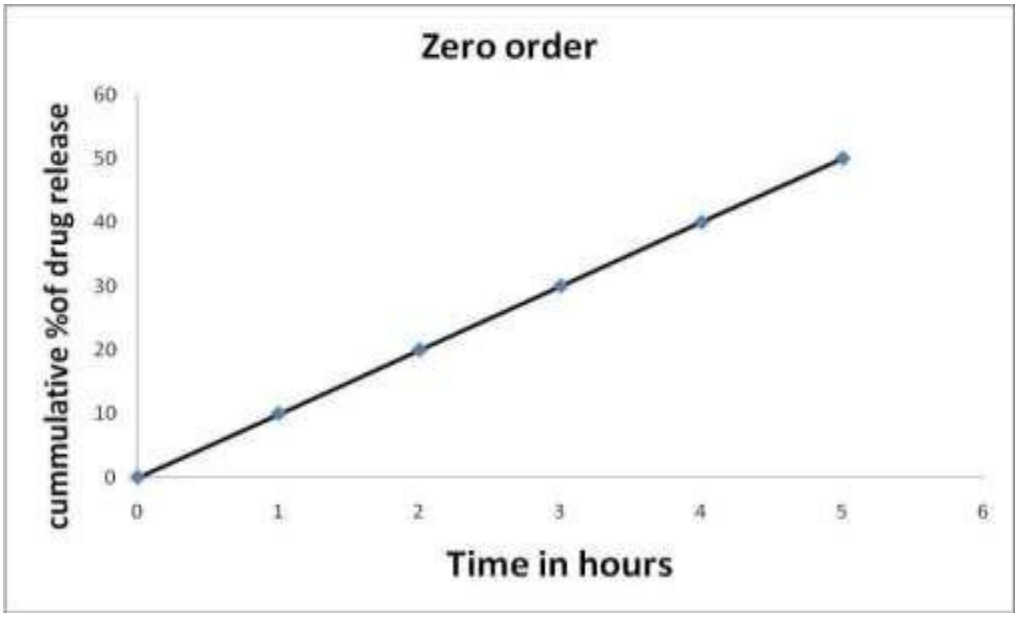

Fig. 4: Zero order kinetics graphs.

B. First Order Release Equation

The first order release equation is **Log Qt = Log Q0+ Kt /2.303**

Where
Q0 = initial amount of drug
Qt = cumulative amount of drug release at time "t"
K = first order release constantt = time in hours

- Here, the drug release rate depends on its concentration.
- A graph is plotted between the time taken on x-axis and the log cumulative percentage of drug remaining to be released on y-axis and it gives a straight line.

C. Higuchi Release Equation

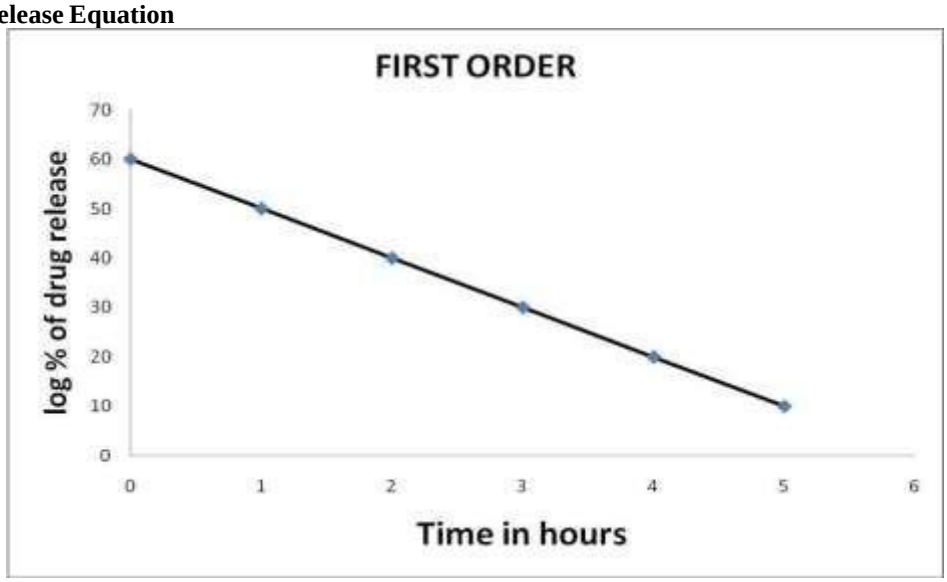

Fig. 5: First order kinetics graphs.

- The Higuchi equation suggests that the drug release
- The Higuchi release equation is **Q=KHt1/2**

Where
Q = cumulative amount of drug release at time "t".KH = Higuchi constantt = time in hours.
by diffusion.

- A graph is plotted between the square root of time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

D. Korsmeyer-Peppas Equation

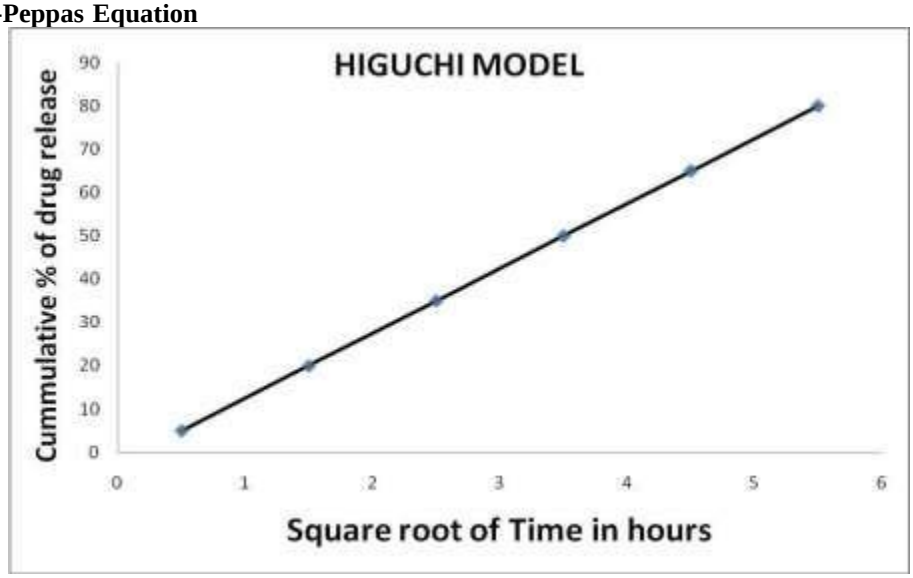

Fig.6: Higuchi Release Equation graphs.

- If n = 0.89 and above indicates case-2 relaxation or Korsmeyer – peppas equation is **F = (Mt /M) = Kmtn**

Where

F = Fraction of drug released at time„t" Mt = Amount of drug released at time„t" M = Total amount of drug in dosage formKm = Kinetic constant

N = Diffusion or release exponentt = Time in hours

- „n" is estimated from linear regression of log (Mt/M) versus log t
- If n = 0.45 indicates fickian diffusion super case transport-2.
- 0.45<n<0.89 indicates anomalous diffusion or non-fickian diffusion.
- Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion controlled rate release.
- Case-2 relaxation or super case transport-2 refers to the erosion of thepolymeric chain.
- A graph is plotted between the log time taken on x-axis and the log cumulative percentage of drug release on y-axis and it gives a straightline.

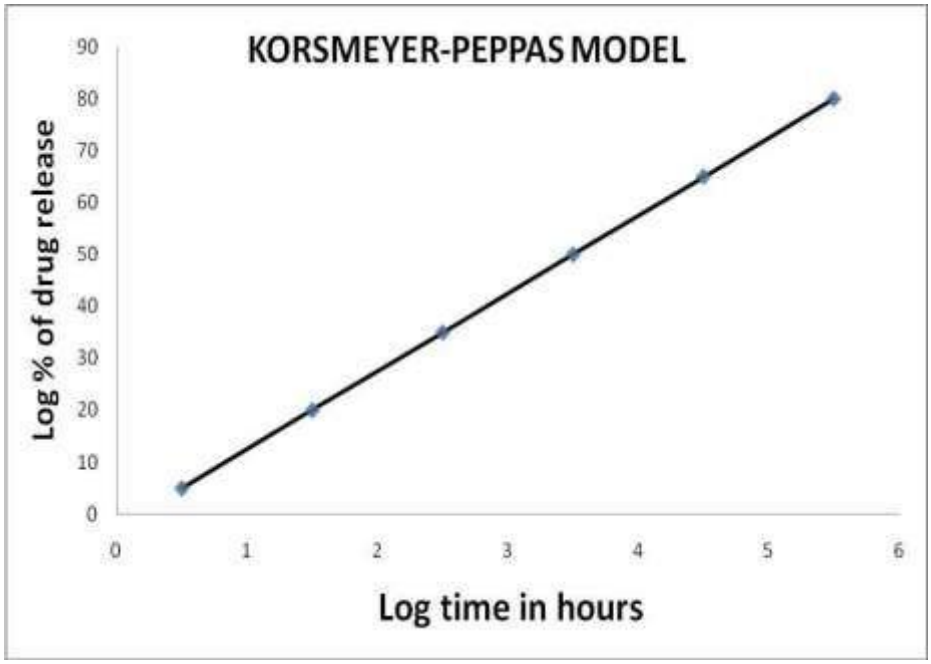

Fig.7: Korsmeyer – peppas equation graphs.

PREFORMULATION STUDIES

LOD studies

The experimental value of Loss on drying for Olmesartan medoxomil is 0.31%. It complies with in the limit of 0.5% It showed that the moisture content present in the sample was within the limit. It confirmed that the drugs were in the pure stable form and it was suitable for the formulation.

ORGANOLEPTIC PROPERTIES

Color : White. Taste : Bitter taste.

Odor : Mild sulfur-like Physical state: Amorphous powderSolubility : 10 mg/ml.

Melting point : 1780C.

SOLUBILITY STUDIES OF OLMESARTAN MEDOXOMIL

Table 12: Solubility studies of olmesartan medoxomil.

Solvent	Olmesartan medoxomil
Water	Insoluble
Methanol	Highly Soluble
Ethanol	Sparingly soluble
Chloroform	Insoluble
DMSO	Soluble
0.1N HCl	Very slightly Soluble
pH 6.8 buffer	Very slightly Soluble
Acetonitrile	Soluble
Acetone	Soluble

The availability of literature on solubility profile of Olmesartan medoxomil indicates that the drugs were freely soluble in methanol. This was confirmed by observing the solubility studies of Olmesartanmedoxomil practically.

COMPATABILITY STUDIESFT-IR STUDY

The FT- IR Spectrum of pure Olmesartan medoxomil drug was compared with that of physical mixture of Olmesartan medoxomil and HPMC 15 cps, Olmesartan medoxomil and Carbopol 940, Olmesartan medoxomil and Lactose. (Fig:). There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

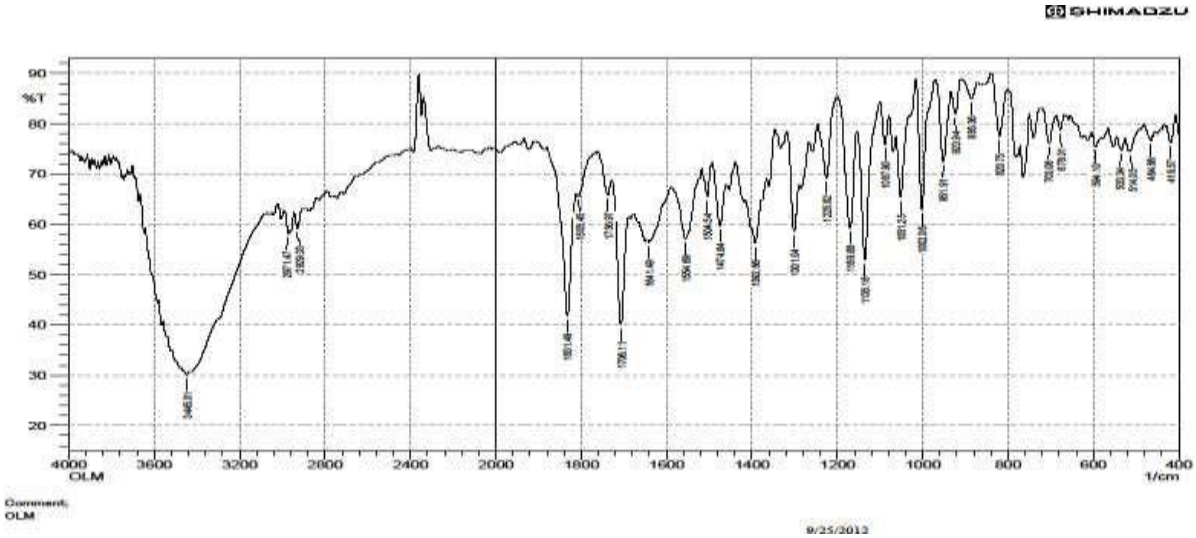

Fig.8: FTIR Spectra of Olmesartan medoxomil.

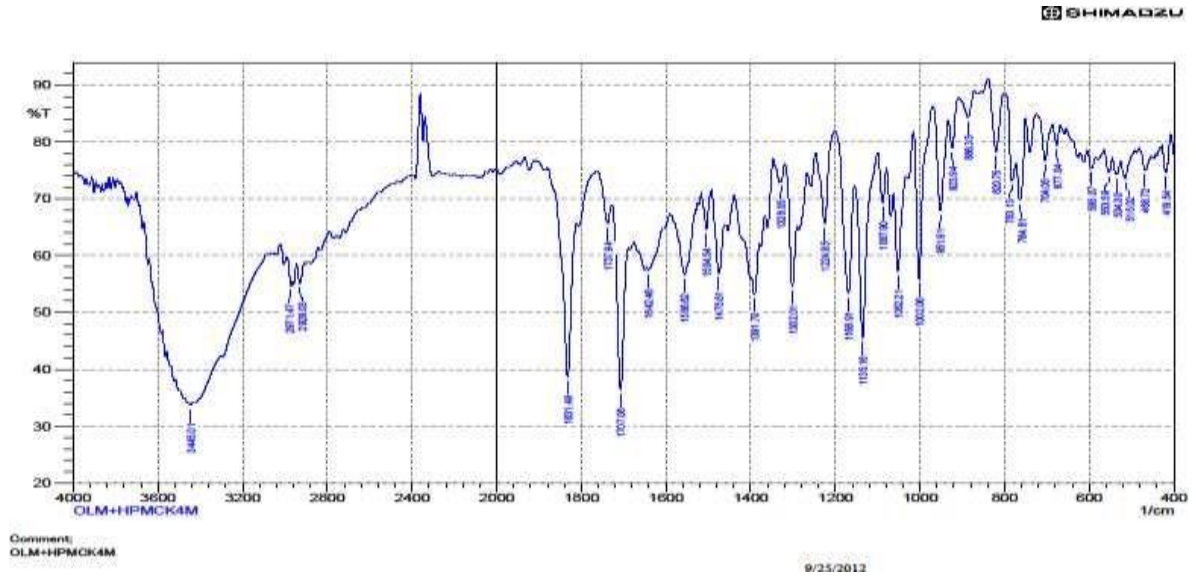

Fig. 9: FTIR Spectra of Olmesartan medoxomil + Hpmc.

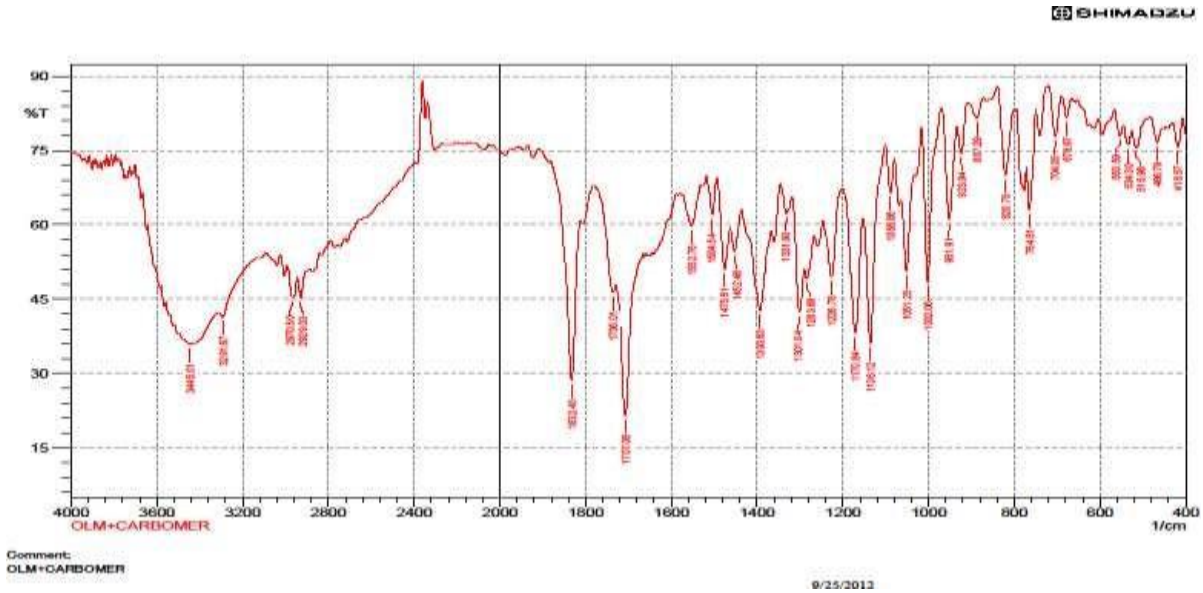

Fig.10: FTIR Spectra of Olmesartan medoxomil + Carbopol.

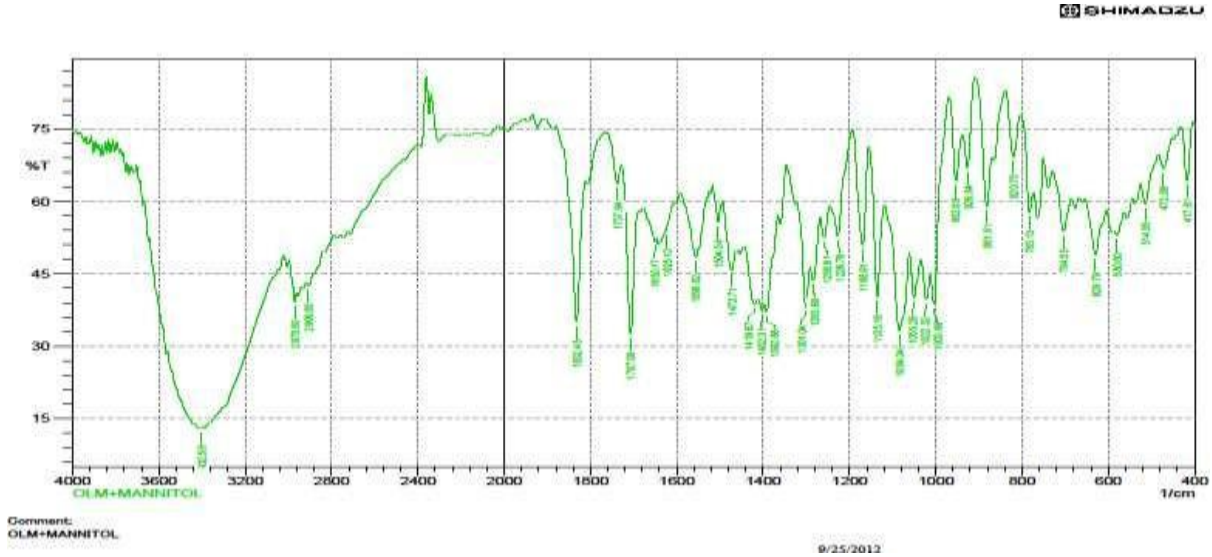

Fig. 11: FTIR Spectra of Olmesartan medoxomil + HPC.

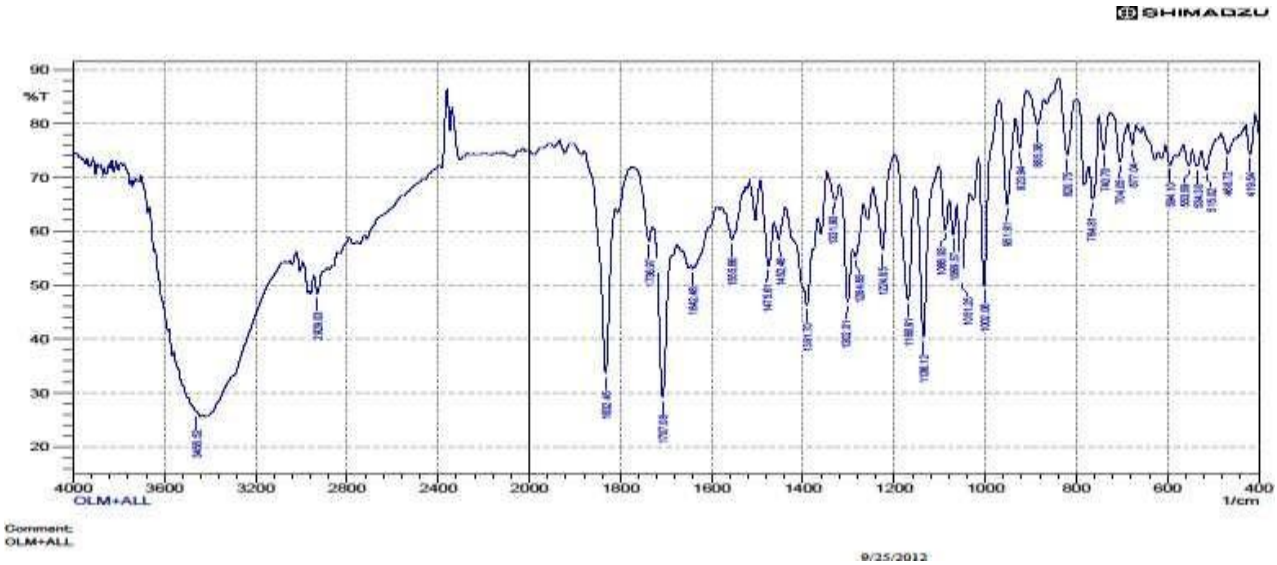

Fig. 12: FTIR Spectra of Optimized formula.

STANDARD CALIBRATION CURVE OF OLMESARTAN MEDOXOMIL

Standard Curve of Olmesartan medoxomil was determined by plotting absorbance (nm) versus concentration (µg/ml) at 255.6 nm. The results obtained are as follows.

Table 13: Standard curve of Olmesartan Medoxomil.

Conc. in µg	Absorbance at 255.6nm
0	0
2	0.119
4	0.245
6	0.367
8	0.488
10	0.603
12	0.726
14	0.848
16	0.98

The linear regression analysis was done on absorbance data points.

A straight-line equation *was* generated to facilitate the calculation of amount of drug. The equation is as follows.

(Y = mx+c)

Where ***Y***= Absorbance, ***m*** = slope, ***x*** = Concentration, ***c*** = Intercept.

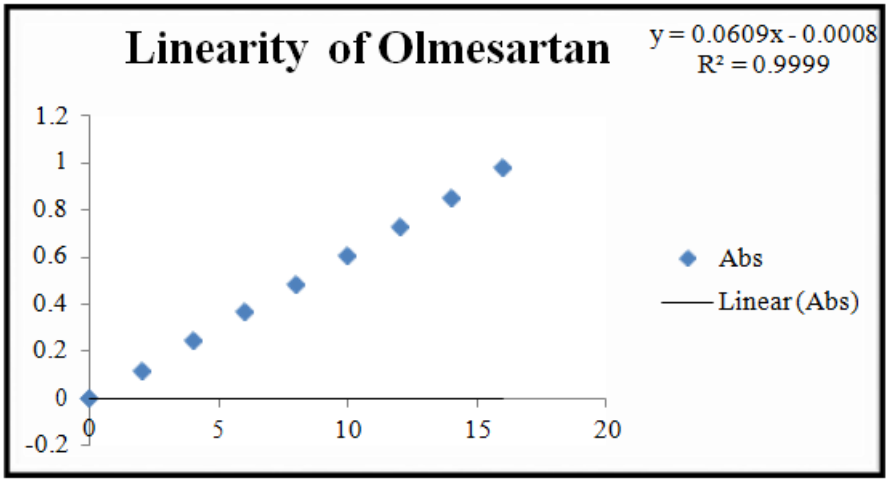

Fig. 13: standard calibration curve of olmesarten medoxomil Table.14 Results of Micromeritic property evaluation.

S.No	Powders/Drugs	Angle of Repose (0) θ=tan-1 (h/r)	Loose bulk Density(LBD) (g/ml)	Tappedbulk Density(TBD) (g/ml)	Carr's index %
1.	Olmesartan medoxomil	270 15‟	0.348	0.421	17.33
2.	OLM+HPMC	260 91‟	0.321	0.372	13.70
3.	OLM + Mannitol	220 01‟	0.318	0.364	12.63

The results of micromeritic properties are presented in the above table. Plain Olmesartan medoxomil exhibited angle of repose value of 27015‟ respectively indicated that the drug contains extremely good flow property. It was further supported by high Carr‟s index value. Hence it was necessary to use suitable filler like mannitol. The incorporation of these fillers into plain drugs improved the flow properties as indicated by reduction in the values of angle of repose and Carr‟s index. But still theexpected good flow property was achieved by all the three vehicles selected, even though the Lactose properties showed possible flow property.

EVALUATION

Various physico chemical properties of Olmesartan medoxomil bydirect compression method.

Table 15: flow properties of formulation.

Formulation	Angle of Repose (0) θ= tan-1(h/r)	Loose bulk Density (LBD) (g/ml)	Tappedbulk Density (TBD) (g/ml)	Carr'sindex %	Hauser's ratio
F1	21004	0.304	0.351	13.41	1.15
F2	21009	0.317	0.367	13.63	1.15
F3	21046	0.310	0.360	13.89	1.16
F4	24088	0.318	0.378	15.87	1.18
F5	24023	0.294	0.346	15.02	1.17
F6	24009	0.307	0.360	14.72	1.17
F7	24078	0.311	0.368	15.21	1.18
F8	24056	0.265	0.312	15.06	1.17
F9	23098	0.332	0.391	14.91	1.17
F10	23002	0.328	0.386	15.02	1.17
F11	24005	0.330	0.376	12.23	1.13
F12	24024	0.335	0.382	12.30	1.14
F13	23008	0.325	0.388	16.23	1.19
F14	23012	0.331	0.386	14.24	1.16
F15	24014	0.328	0.380	13.68	1.15

DISCUSSION

From the above tables, it was confirmed that both the drugs were exhibited excellent flow property (AOR= 20 to 24), when the drug was powder with excipients. It was also supported with the results of Carr"s index value.

RESULTS OF TABLET EVALUATION

Table 16: Dissolution studies of Formulation F1-F15.

	1hr	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr
F1	27.23	41.9	66.12	91.86	96.18	--	--	--	--
F2	22.54	35.12	50.34	63.87	77.02	96.56	--	--	-
F3	18.03	27.8	37.76	51.47	64.43	78.9	91.86	96.74	--
F4	37.42	61.94	94.77	--	--	--	--	--	--
F5	24.44	35.82	49.44	70.89	85.82	95.34	--	--	--
F6	19.6	32.46	50.56	65.67	78.36	89.55	96.26	---	--
F7	34.32	55.22	75.74	89.18	97.01	--	--	--	--
F8	28.73	45.9	61.94	73.5	85.07	95.9	--	--	--
F9	17.16	26.86	36.94	48.88	60.44	69.4	78.54	87.31	98.5
F10	23.88	32.46	47.76	72.57	95.52	--	--	--	--
F11	21.26	28.73	43.65	61.56	87.31	97.2	--	--	--
F12	16.23	24.99	33.76	51.11	66.23	87.87	98.13	--	--
F13	25.37	41.6	55.59	80.41	94.02	97.76	--	--	--
F14	28.73	32.46	46.08	56.15	71.26	80.22	91.6	96.82	--
F15	17.72	26.86	36.19	43.47	57.64	69.77	78.54	90.67	97.94

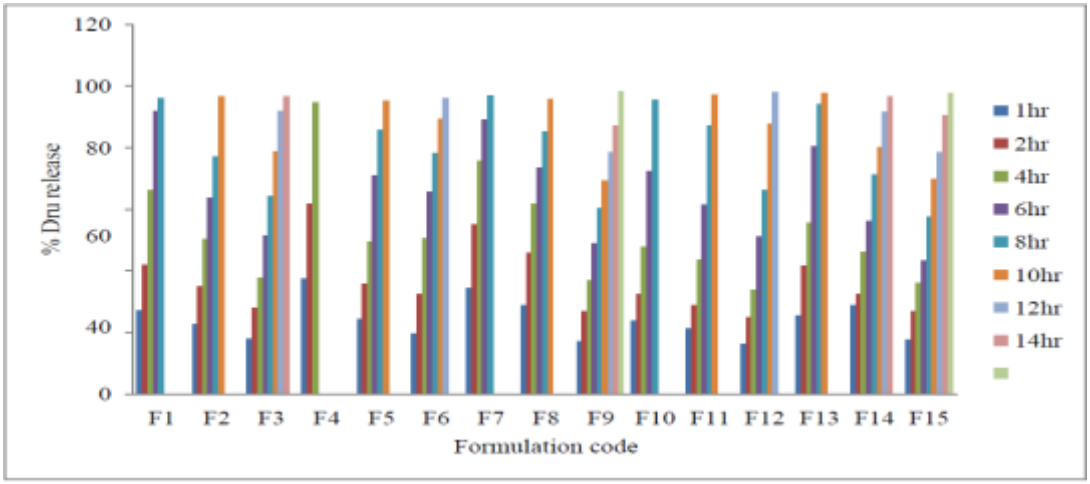

Fig.14: Dissolution profile of Formulation F1 to F15.

The results of *in-vitro* drug release studies in 0.1N HCl Fig. Initially our aim was to select optimum concentration of HPMC, HPC and Carbopol of different grades for floating tablets.

Hence the tablets containing,

- Floating layer of Olmesartan medoxomil was prepared by altering the concentration of different grade of HPMC, HPC and Carbopol934p.
- The maximum drug release was found to be formulation contains HPMC k15m (20%) i.e., F9 (98.5%).

Discussion for *in-vitro* release of Olmesartan medoxomil floatinglayer

In the above table contains the release studies of floating layer of Olmesartan medoxomil, in that the Formulation F1 to F3 contains the concentration of polymer 5%, Formulation F4 to F6 Contains 10% concentration of polymer and F7 to F9 Were contains 15% concentration of polymer.

In the dissolution profile, the concentration of polymer increases the drug release profile decreases.

- The formulation F1, F4, F7, F10 and F13 having 10% concentration of HPMC k4m, k100m, k15m, HPC and Carbopol showing 94.77 to 97.76 % drug release with respect of time.
- the formulation F2, F5, F8, F11, and F14 having 10% concentration of POLYMER showing 96.56%, 95.34%, 95.09%, 97.20% and 96.8% drug release with respect of time.
- the formulation F3, F6, F9, F12, F15 having 20% concentration of polymer showing 96.74%, 96.26%, 98.5%, 89.13% and 97.64% drug release with respect of time.

Table 17: Floating time of tablet.

Formulation code	L.F.T (sec) {buoyancy time}	T.F.T (hrs)
F1	65	8
F2	72	12
F3	83	16
F4	69	5
F5	82	11
F6	93	12
F7	75	10
F8	89	12
F9	102	18
F10	64	10
F11	76	11
F12	99	14
F13	96	12
F14	124	16
F15	154	20

Table 18: Evaluation Parameters.

Formulation	Uniformity of Weightmg	Hardness Kg/cm2	Diameter (mm)	Friability (%)	Drug content (%)
F1	201	5.1	8.7	0.435	98.70
F2	200	5.4	8.7	0.492	99.25
F3	199	5.3	8.7	0.501	99.42
F4	200	5.5	8.7	0.463	98.52
F5	201	5	8.7	0.478	98.24
F6	202	5.2	8.7	0.342	98.63
F7	198	5.5	8.7	0.414	98.15
F8	200	5.5	8.7	0.417	99.42
F9	200	5.2	8.7	0.318	99.14
F10	198	5.1	8.7	0.412	98.46
F11	199	5.2	8.7	0.416	98.10
F12	204	5.2	8.7	0.514	98.65
F13	201	5.1	8.7	0.355	98.32
F14	198	5.3	8.7	0.411	98.65
F15	202	5.1	8.7	0.441	98.02

DISCUSSION

From the above table, the results showed that all trial tablets have their weight within 198 to 204 mg/ tablet. The formulation Trial 1 and Trial 15, all trials have the sufficient hardness i.e., with in the limit. Allthe tablets of different trials were uniform in diameter (8.7 mm). According to Friability parameter, the tablets of trials F1 and F15 trials were within the prescribed limits i.e., (<1). Good and Uniform drug content (>98%) was observed within the batches of different tablet formulations. Hence the tablets contain floating layer of drug (Olmesartan medoxomil), HPMC (K4m, K100m and K15m), HPC and Carbomer and other excipients mentioned in the table.

KINETIC DATA

Zero order kinetics

Table 19: Zero order kinetics data For F9.

Time inhrs	1	2	4	6	8	10	12	14	16
% CDR	17.16	26.86	36.94	48.88	60.44	69.4	78.54	87.31	98.5

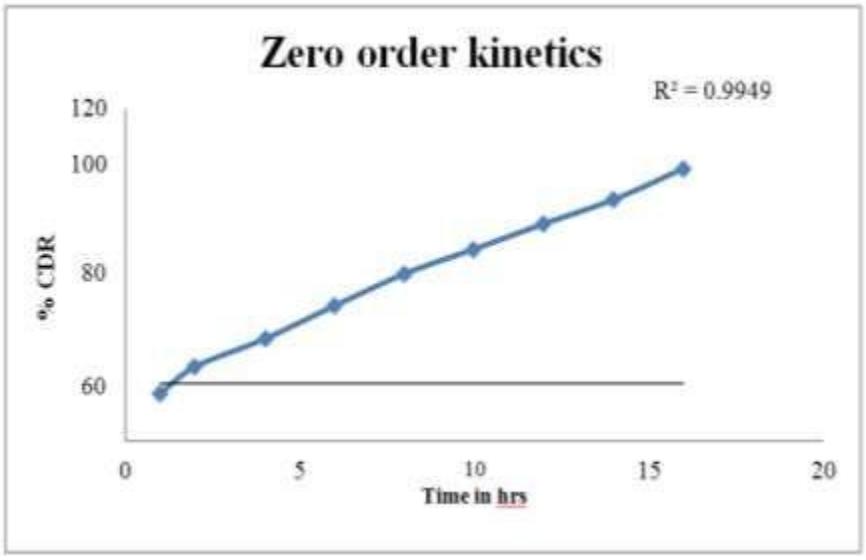

Fig. 15: Graphical Representation of Zero Order Release.

First Order kinetics

Table 21: First order kinetics data For F9.

Time	1	2	4	6	8	10	12	14	16
Log%remaining	1.918	1.864	1.799	1.708	1.597	1.477	1.331	1.103	0.178

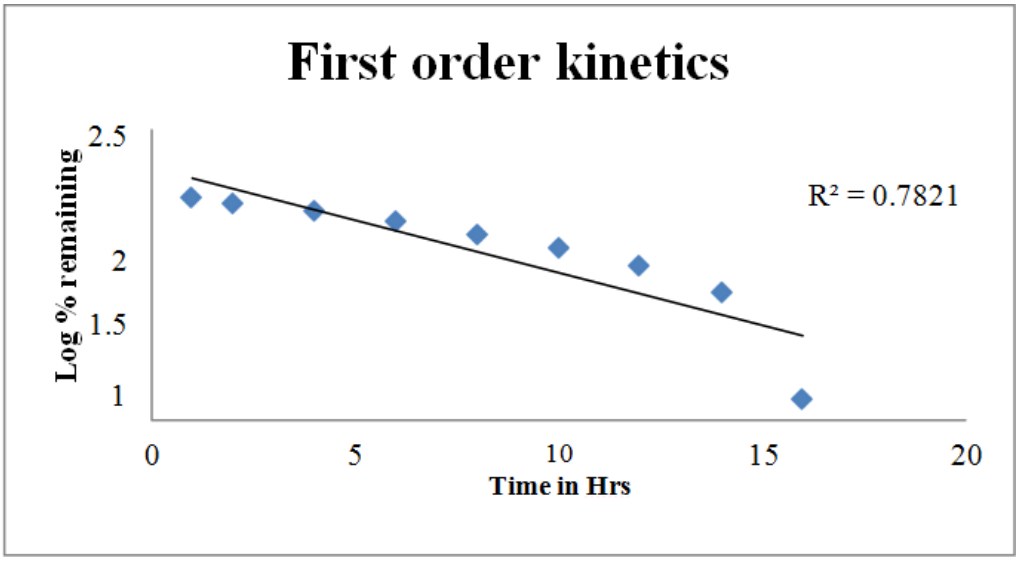

Fig.16: Graphical representation of First Order Release.

Higuchi Model

Table 22: Higuchi model kinetic data for F9.

SQRT	1	1.414	2	2.449	2.828	3.162	3.464	3.741	4
% CDR	17.16	26.86	36.94	48.88	60.44	69.4	78.54	87.31	98.5

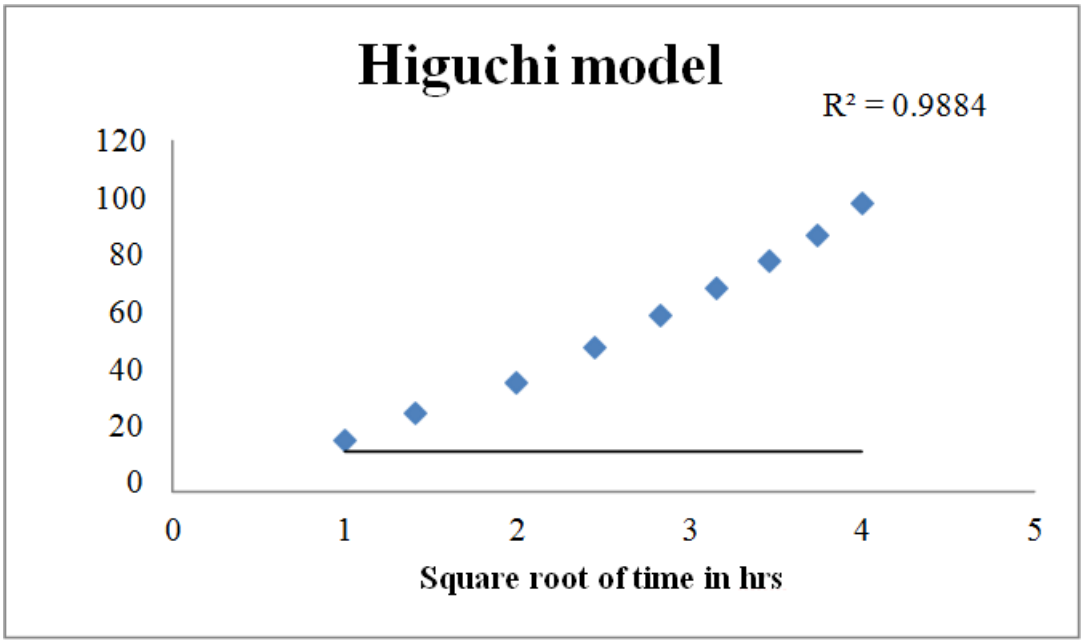

Fig. 17: Graphical representation of Higuchi model.

Korsmeyer Peppas

Table 23: Korsmeyer peppas kinetic data for F9.

Log time	0	0.301	0.302	0.778	0.903	1	1.079	1.146	1.204
Log % CDR	1.234	1.429	1.567	1.689	1.781	1.84	1.895	1.941	1.993

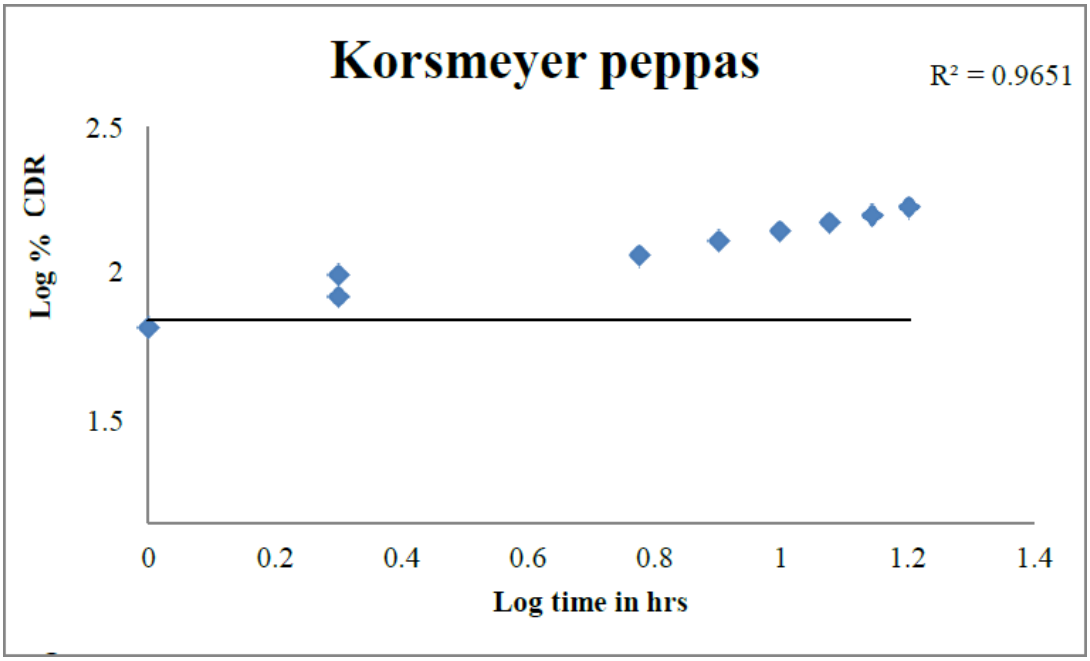

Fig.18: Graphical Representation of Korsmeyer Peppas.

DISCCUSION

The kinetic investigation of the release profile gave us useful insight into the mechanism of drug release from the tablets. The release did not show any burst effect or lag time, which is indicative of a homogeneous drug distribution in the polymer matrix. The dissolution data was subjected to regression analysis and were fitted to kinetic models, viz., Zero order, First order, Peppas and

Higuchi. It was found that most of the formulations followed Zero order (0.994) and Higuchi release (R2=0.988).

- Zero order release describes the systems where the drug release rate is independent of its concentration of the dissolved substance.
- The Higuchi equation suggests that the drug release by diffusion.

SUMMARY AND CONCLUSION

The Olmesartan Medoxomil is a selective ACE-II blocking agent which is used in the treatment of hypertension. In this study Olmesartan Medoxomil tablets were prepared by using different polymers like HPMCK4M, HPMCK15M, HPMCK100M and CARBOPOL and HPC.

Fifteen formulations of floating tablets of Olmesartan Medoxomil were developed by direct compression technique. The F9 formulation was found to be best of all the trials showing that the drug release matches with the brand product.

The best formulation F9 can successfully be employed as a controlled release floating drug delivery system. The floating tablets can control the fluctuations in the plasma drug concentration, increase the gastric residence time and eventually improve the bioavailability of the drug.

The FTIR study ruled out the drug-polymer interaction.

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